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NEWS 1		Web Page for STN Seminar Schedule - N. America
NEWS 2	DEC 01	ChemPort single article sales feature unavailable
NEWS 3	JUN 01	CAS REGISTRY Source of Registration (SR) searching enhanced on STN
NEWS 4	JUN 26	NUTRACEUT and PHARMAML no longer updated
NEWS 5	JUN 29	IMSCOPROFILE now reloaded monthly
NEWS 6	JUN 29	EPFULL adds Simultaneous Left and Right Truncation (SLART) to AB, MCLM, and TI fields
NEWS 7	JUL 09	PATDPAFULL adds Simultaneous Left and Right Truncation (SLART) to AB, CLM, MCLM, and TI fields
NEWS 8	JUL 14	USGENE enhances coverage of patent sequence location (PSL) data
NEWS 9	JUL 27	CA/CAplus enhanced with new citing references
NEWS 10	JUL 16	GBFULL adds patent backfile data to 1855
NEWS 11	JUL 21	USGENE adds bibliographic and sequence information
NEWS 12	JUL 28	EPFULL adds first-page images and applicant-cited references
NEWS 13	JUL 28	INPADOCDB and INPAFAMDB add Russian legal status data
NEWS 14	AUG 08	Improve STN by completing a survey and be entered to win a gift card
NEWS 15	AUG 10	Time limit for inactive STN sessions doubles to 40 minutes
NEWS 16	AUG 17	CAS REGISTRY, the Global Standard for Chemical Research, Approaches 50 Millionth Registration Milestone

NEWS EXPRESS MAY 26 09 CURRENT WINDOWS VERSION IS V8.4,
AND CURRENT DISCOVER FILE IS DATED 06 APRIL 2009.

NEWS HOURS STN Operating Hours Plus Help Desk Availability
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* http://www.zoomerang.com/Survey/?p=WEB229H4S8Q5UL                    *
*                                                                      *
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* * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 15:58:06 ON 17 AUG 2009

=> file registry
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.22       0.22

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STRUCTURE FILE UPDATES:   16 AUG 2009  HIGHEST RN 1174375-84-8
DICTIONARY FILE UPDATES:  16 AUG 2009  HIGHEST RN 1174375-84-8

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TSCA INFORMATION NOW CURRENT THROUGH June 26, 2009.

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experimental property data in the original document.  For information
on property searching in REGISTRY, refer to:

http://www.cas.org/support/stngen/stndoc/properties.html

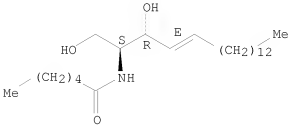
=> s c6-ceramide/cn
L1            1 C6-CERAMIDE/CN

=> d l1

L1   ANSWER 1 OF 1  REGISTRY  COPYRIGHT 2009 ACS on STN
RN   124753-97-5  REGISTRY
ED   Entered STN:  19 Jan 1990
CN   Hexanamide, N-[(1S,2R,3E)-2-hydroxy-1-(hydroxymethyl)-3-heptadecen-1-yl]-
     (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   Hexanamide, N-[(1S,2R,3E)-2-hydroxy-1-(hydroxymethyl)-3-heptadecenyl]-
     (9CI)
CN   Hexanamide, N-[2-hydroxy-1-(hydroxymethyl)-3-heptadecenyl]-,
     [R-[R*,S*-(E)]]-
OTHER NAMES:
CN   C6-Ceramide
CN   D-erythro-C6-Ceramide
CN   N-Caproyl-C18-sphingosine
CN   N-Hexanoyl-D-erythro-sphingosine
CN   N-Hexanoylsphingosine
FS   STEREOSEARCH
```

MF C24 H47 N O3
SR CA
LC STN Files: AGRICOLA, BIOSIS, CA, CAPLUS, CASREACT, CHEMCATS, CIN, CSCHEM, TOXCENTER, USPAT2, USPATFULL

Absolute stereochemistry.
Double bond geometry as shown.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

252 REFERENCES IN FILE CA (1907 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
252 REFERENCES IN FILE CAPLUS (1907 TO DATE)

=> file caplus

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	7.88	8.10

FILE 'CAPLUS' ENTERED AT 15:58:44 ON 17 AUG 2009
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FILE COVERS 1907 - 17 Aug 2009 VOL 151 ISS 8
FILE LAST UPDATED: 16 Aug 2009 (20090816/ED)
REVISED CLASS FIELDS (/NCL) LAST RELOADED: Jun 2009
USPTO MANUAL OF CLASSIFICATIONS THESAURUS ISSUE DATE: Jun 2009

CAplus now includes complete International Patent Classification (IPC) reclassification data for the second quarter of 2009.

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http://www.cas.org/legal/infopolicy.html

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This file contains CAS Registry Numbers for easy and accurate
substance identification.

The ALL, BIB, MAX, and STD display formats in the CA/CAplus family
of databases have been updated to include new citing references
information.  This enhancement may impact record import into
database management software.  For additional information, refer
to NEWS 9.

=> s l1
L2         252 L1

=> s l2 and (?cancer? or ?tumor? or ?tumour? or ?neoplasm?)
        467812 ?CANCER?
        738311 ?TUMOR?
          6470 ?TUMOUR?
          6470 ?TUMOUR?
        738690 ?TUMOR?
                 (?TUMOR? OR ?TUMOUR?)
          6470 ?TUMOUR?
        738311 ?TUMOR?
        738311 ?TUMOR?
        738690 ?TUMOUR?
                 (?TUMOUR? OR ?TUMOR?)
        574533 ?NEOPLASM?
L3          85 L2 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM?)

=> s l3 and ad<19990407
       3535330 AD<19990407
                 (AD<19990407)
L4           3 L3 AND AD<19990407

=> d l4 1-3 ibib abs

L4   ANSWER 1 OF 3  CAPLUS  COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER:         1996:509392  CAPLUS
DOCUMENT NUMBER:          125:132742
ORIGINAL REFERENCE NO.:   125:24597a,24600a
TITLE:                    Sphingosine and N-methylated sphingosine derivatives
                          for induction of apoptosis
INVENTOR(S):              Igarashi, Yasuyuki; Hakomori, Sen-Itiroh
PATENT ASSIGNEE(S):       Biomembrane Institute, USA
SOURCE:                   PCT Int. Appl., 40 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   3
PATENT INFORMATION:

     PATENT NO.          KIND   DATE        APPLICATION NO.        DATE
     --------------      ----   --------    -------------------    --------
     WO 9618404           A1    19960620    WO 1995-US5019         19950428 <--
         W:  CA, JP
         RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
     US 5583160           A     19961210    US 1994-357306         19941214 <--
     EP 812199            A1    19971217    EP 1995-917649         19950428 <--
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE
     JP 10510805          T     19981020    JP 1995-518725         19950428 <--
PRIORITY APPLN. INFO.:                     US 1994-357306      A  19941214
                                           US 1989-306378      B2 19890203
                                           US 1989-390135      B1 19890807
                                           US 1992-965614      A2 19921022
```

WO 1995-US5019 W 19950428

AB Sphingosine, and N-methylated derivs. thereof (e.g. dimethylsphingosine), are disclosed for inducing apoptosis. The sphingosine or sphingosine derivative may be contained in a liposome. The effect of sphingosine and related compds. was tested in a variety of cells, including tumor cells. In mice injected with the metastatic and invasive BL6 cell line, treatment with liposomes containing dimethylsphingosine reduced tumor development and colony development.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1996:464360 CAPLUS

DOCUMENT NUMBER: 125:105139

ORIGINAL REFERENCE NO.: 125:19435a,19438a

TITLE: N-acylsphingosine and sphingomyelinase as inhibitors of neuron degeneration and death

INVENTOR(S): Ito, Akira

PATENT ASSIGNEE(S): Sumitomo Pharmaceuticals Co., Ltd., Japan

SOURCE: Jpn. Kokai Tokkyo Koho, 5 pp.
CODEN: JKXXAF

DOCUMENT TYPE: Patent

LANGUAGE: Japanese

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 08113535	A	19960507	JP 1994-276077	19941013 <--
PRIORITY APPLN. INFO.:			JP 1994-276077	19941013

AB N-acylsphingosine and sphingomyelinase are claimed as inhibitors of neuron degeneration and death from mech. injury, neuropathy from antitumor agents, or pathol. conditions e.g. from Alzheimer's disease, parkinsonism, hypotrophic muscular disease, and diabetic neuropathy. Thus, N-acetylsphingosine inhibited neuron death in cultured rat fetal ganglia.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

L4 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 1995:958040 CAPLUS

DOCUMENT NUMBER: 124:768

ORIGINAL REFERENCE NO.: 124:167a,170a

TITLE: Pharmaceutically active sphingolipid compounds, liposomes containing them, and methods of use, especially for treatment of cancer

INVENTOR(S): Pei, Yong-Wei; Mayhew, Eric; Ahmad, Imran; Janoff, Andrew S.

PATENT ASSIGNEE(S): Liposome Co., Inc., USA

SOURCE: PCT Int. Appl., 64 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9521175	A1	19950810	WO 1995-US1490	19950202 <--
W: AU, CA, FI, JP, KR, NO				

```
        RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE
     CA 2182485          A1    19950810    CA 1995-2182485          19950202 <--
     AU 9518712          A     19950821    AU 1995-18712            19950202 <--
     AU 691886           B2    19980528
     EP 742789           A1    19961120    EP 1995-910923           19950202 <--
     EP 742789           B1    20000830
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
     JP 09508900         T     19970909    JP 1995-520799           19950202 <--
     EP 1008342          A2    20000614    EP 2000-102434           19950202 <--
     EP 1008342          A3    20041229
        R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE
     AT 195944           T     20000915    AT 1995-910923           19950202 <--
     ES 2149350          T3    20001101    ES 1995-910923           19950202 <--
     FI 9603045          A     19960801    FI 1996-3045             19960801 <--
     FI 116620           B1    20060113
     NO 9603224          A     19960927    NO 1996-3224             19960801 <--
     NO 314405           B1    20030317
     GR 3034521          T3    20001229    GR 2000-402211           20000929
PRIORITY APPLN. INFO.:                      US 1994-190295      A    19940202
                                            EP 1995-910923      A3   19950202
                                            WO 1995-US1490      W    19950202

OTHER SOURCE(S):         MARPAT 124:768
AB   Compds. R1Y1CHZ1CH(NY2Y3)CH2Z2 [R1 = straight-chain C8-19 alkyl, alkenyl
     or alkynyl; Y1 = CH=CH, C||C, CH(OH)CH(OH); Z1 = OH, conversion-inhibiting
     group; Z2 = conversion-inhibiting group; Y2 = H, Ph, (C1-6
     alkyl)-substituted Ph, C1-6 alkyl; Y3 = H, C(O)R2, -S(O)2R2; R2 =
     straight-chain C1-23 alkyl, alkenyl or alkynyl; when Z2 = amino, R2 = C1-9
     or C19-23 aliphatic chain] are disclosed, as are liposomes containing such
     compds.  Methods for treating cancer using the compds. and
     liposomes of the invention are also disclosed.  The effect of e.g. various
     liposomal ceramide/sphingomyelin formulations on the growth of e.g. HL-60
     cells was determined
OS.CITING REF COUNT:     4     THERE ARE 4 CAPLUS RECORDS THAT CITE THIS RECORD
                               (6 CITINGS)


=> d his

     (FILE 'HOME' ENTERED AT 15:58:06 ON 17 AUG 2009)

     FILE 'REGISTRY' ENTERED AT 15:58:30 ON 17 AUG 2009
L1             1 S C6-CERAMIDE/CN

     FILE 'CAPLUS' ENTERED AT 15:58:44 ON 17 AUG 2009
L2           252 S L1
L3            85 S L2 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM?)
L4             3 S L3 AND AD<19990407

=> s l3 and (paclitaxel or taxol)
         14425 PACLITAXEL
            20 PACLITAXELS
         14425 PACLITAXEL
                 (PACLITAXEL OR PACLITAXELS)
          9607 TAXOL
            49 TAXOLS
          9613 TAXOL
                 (TAXOL OR TAXOLS)
L5            13 L3 AND (PACLITAXEL OR TAXOL)

=> d l5 1-13 ibib abs

L5   ANSWER 1 OF 13  CAPLUS  COPYRIGHT 2009 ACS on STN
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ACCESSION NUMBER: 2008:1528599 CAPLUS
DOCUMENT NUMBER: 150:208289
TITLE: Acid Ceramidase Upregulation in Prostate Cancer Cells Confers Resistance to Radiation: AC Inhibition, a Potential Radiosensitizer
AUTHOR(S): Mahdy, Ayman E. M.; Cheng, Joseph C.; Li, Jun; Elojeimy, Saeed; Meacham, William D.; Turner, Lorianne S.; Bai, Aiping; Gault, Christopher R.; McPherson, Alex S.; Garcia, Nicole; Beckham, Thomas H.; Saad, Antonio; Bielawska, Alicja; Bielawski, Jacek; Hannun, Yusuf A.; Keane, Thomas E.; Taha, Mohhammed I.; Hammouda, Hisham M.; Norris, James S.; Liu, Xiang
CORPORATE SOURCE: Department of Microbiology and Immunology, Medical University of South Carolina, Charleston, SC, 29425, USA
SOURCE: Molecular Therapy (2009), 17(3), 430-438
CODEN: MTOHCK; ISSN: 1525-0016
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Radiation resistance in a subset of prostate tumors remains a challenge to prostate cancer radiotherapy. The current study on the effects of radiation on prostate cancer cells reveals that radiation programs an unpredicted resistance mechanism by upregulating acid ceramidase (AC). Irradiated cells demonstrated limited changes of ceramide levels while elevating levels of sphingosine and sphingosine-1-phosphate. By genetically downregulating AC with small interfering RNA (siRNA), we observed radiosensitization of cells using clonogenic and cytotoxicity assays. Conversely, AC overexpression further decreased sensitivity to radiation. We also observed that radiation-induced AC upregulation was sufficient to create cross-resistance to chemotherapy as demonstrated by decreased sensitivity to Taxol and C6 ceramide compared to controls. Lower levels of caspase 3/7 activity were detected in cells pretreated with radiation, also indicating increased resistance. Finally, utilization of the small mol. AC inhibitor, LCL385, sensitized PPC-1 cells to radiation and significantly decreased tumor xenograft growth. These data suggest a new mechanism of cancer cell resistance to radiation, through upregulation of AC i.e., in part, mediated by application of the therapy itself. An improved understanding of radiotherapy and the application of combination therapy achieved in this study offer new opportunities for the modulation of radiation effects in the treatment of cancer.
REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 2 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2008:837538 CAPLUS
DOCUMENT NUMBER: 149:135745
TITLE: Biodistribution and Pharmacokinetic Analysis of Paclitaxel and Ceramide Administered in Multifunctional Polymer-Blend Nanoparticles in Drug Resistant Breast Cancer Model
AUTHOR(S): van Vlerken, Lilian E.; Duan, Zhenfeng; Little, Steven R.; Seiden, Michael V.; Amiji, Mansoor M.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, Northeastern University, Boston, MA, USA
SOURCE: Molecular Pharmaceutics (2008), 5(4), 516-526
CODEN: MPOHBP; ISSN: 1543-8384
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In this study, we have investigated the biodistribution and

pharmacokinetic anal. of paclitaxel (PTX) and the apoptotic signaling mol., C6-ceramide (CER), when administered in a multifunctional polymer-blend nanoparticle formulation to female nude mice bearing an orthotopic drug sensitive MCF7 and multidrug resistant MCF7TR (MDR-1 pos.) human breast adenocarcinoma. A polymer-blend nanoparticle system was engineered to incorporate temporally controlled sequential release of the combination drug payload. Hereby, PTX was encapsulated in the pH-responsive rapid releasing polymer, poly(beta-amino ester) (PbAE), while CER was present in the slow releasing polymer, poly(D,L-lactide-co-glycolide) (PLGA) within these blend nanoparticles. When particle formulations were administered i.v. to MCF7 and MCF7TR tumor bearing mice, higher concns. of PTX were found in the blood due to longer retention time and an enhanced tumor accumulation relative to administration of free drug. In addition, the PLGA/PbAE blend nanoparticles were effective in enhancing the residence time of both drugs at the tumor site by reducing systemic clearance. Overall, these results are highly encouraging for development of multifunctional polymer-blend nanoparticle formulations that can be used for temporal-controlled administration of two drugs from a single formulation.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 3 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2008:819602 CAPLUS

DOCUMENT NUMBER: 149:315240

TITLE: Cytotoxicity and apoptosis enhancement in brain tumor cells upon coadministration of paclitaxel and ceramide in nanoemulsion formulations

AUTHOR(S): Desai, Ankita; Vyas, Tushar; Amiji, Mansoor

CORPORATE SOURCE: Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, Boston, MA, 02115, USA

SOURCE: Journal of Pharmaceutical Sciences (2008), 97(7), 2745-2756
CODEN: JPMSAE; ISSN: 0022-3549

PUBLISHER: Wiley-Liss, Inc.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The objective of this study was to examine augmentation of therapeutic activity in human glioblastoma cells with combination of paclitaxel (PTX) and the apoptotic signaling mol., C6-ceramide (CER), when administered in novel oil-in-water nanoemulsions. The nanoemulsions were formulated with pine-nut oil, which has high concns. of essential polyunsatd. fatty acid (PUFA). Drug-containing nanoemulsions were characterized for particle size, surface charge, and the particle morphol. was examined with transmission electron microscopy (TEM). Epi-fluorescent microscopy was used to analyze nanoemulsion-encapsulated rhodamine-labeled PTX and NBD-labeled CER uptake and distribution in U-118 human glioblastoma cells. Cell viability was assessed with the MTS (formazan) assay, while apoptotic activity of PTX and CER was evaluated with caspase-3/7 activation and flow cytometry. Nanoemulsion formulations with the oil droplet size of approx. 200 nm in diameter were prepared with PTX, CER, and combination of the two agents. When administered to U-118 cells, significant enhancement in cytotoxicity was observed with combination of PTX and CER as compared to administration of individual agents. The increase in cytotoxicity correlated with enhancement in apoptotic activity in cells treated with combination of PTX and CER. The results of these studies show that oil-in-water nanoemulsions can be designed with combination therapy for enhancement of cytotoxic effect in brain tumor

cells. In addition, PTX and CER can be used together to augment therapeutic activity, especially in aggressive tumor models such as glioblastoma.

OS.CITING REF COUNT: 1 THERE ARE 1 CAPLUS RECORDS THAT CITE THIS RECORD (1 CITINGS)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 4 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2007:1420210 CAPLUS

DOCUMENT NUMBER: 148:24415

TITLE: ceramide and oxaliplatin combination for cancer therapy

INVENTOR(S): Wanebo, Harold J.

PATENT ASSIGNEE(S): Roger Williams Hospital, USA

SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007143175	A2	20071213	WO 2007-US13077	20070531
WO 2007143175	A3	20080131		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW			
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA			
US 20080033039	A1	20080207	US 2007-809418	20070531
EP 2038248	A2	20090325	EP 2007-795674	20070531
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, RS				
PRIORITY APPLN. INFO.:			US 2006-810243P	P 20060602
			WO 2007-US13077	W 20070531

AB This invention provides a method for increasing apoptosis in a cancer cell comprising contacting the cancer cell with (a) oxaliplatin and (b) C6-ceramide, sequentially or concomitantly, wherein the oxaliplatin and C6-ceramide are in amts. such that the apoptosis induced by the combination of oxaliplatin and C6-ceramide is greater than the apoptosis induced by contacting the cancer cell with either oxaliplatin alone or C6-ceramide alone. This invention also provides a method of decreasing the size of a tumor, which method comprises contacting the tumor with (a) oxaliplatin and (b) C6-ceramide, sequentially or concomitantly, wherein the oxaliplatin and C6-ceramide are in amts. such that the decrease in tumor size induced by the combination of oxaliplatin and C6-ceramide is greater than the decrease in tumor size induced by contacting the tumor with either oxaliplatin alone or C6-ceramide alone. This invention further provides a pharmaceutical composition and a method for treating a subject afflicted with cancer.

L5 ANSWER 5 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2007:1087710 CAPLUS
DOCUMENT NUMBER: 147:496093
TITLE: Paclitaxel and ceramide co-administration in biodegradable polymeric nanoparticulate delivery system to overcome drug resistance in ovarian cancer
AUTHOR(S): Devalapally, Harikrishna; Duan, Zhenfeng; Seiden, Michael V.; Amiji, Mansoor M.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, School of Pharmacy, Northeastern University, Boston, MA, USA
SOURCE: International Journal of Cancer (2007), 121(8), 1830-1838
CODEN: IJCNAW; ISSN: 0020-7136
PUBLISHER: Wiley-Liss, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective of this study was to overcome drug resistance upon systemic administration of combination paclitaxel (PTX) and the apoptotic signaling mol. C6-ceramide (CER) in biodegradable poly(ethylene oxide)-modified poly(epsilon-caprolactone) (PEO-PCL) nanoparticles. S.c. sensitive (wild-type) and multidrug resistant (MDR-1 pos.) SKOV-3 human ovarian adenocarcinoma xenografts were established in female Nu/Nu mice. PTX and CER were administered i.v. either as a single agent or in combination in aqueous solution and in PEO-PCL nanoparticles to the tumor -bearing mice. There was significant ($p < 0.05$) tumor growth suppression in both wild-type SKOV-3 and multidrug resistant SKOV-3TR models upon single dose co-administration of PTX (20 mg/kg) and CER (100 mg/kg) in nanoparticle formulations as compared to the individual agents and administration in aqueous solns. For instance, in SKOV-3 wild-type model, more than 4.3-fold increase ($p < 0.05$) in tumor growth delay and 3.6-fold ($p < 0.05$) increase in tumor volume doubling time (DT) were observed with the combination treatment in nanoparticles as compared to untreated animals. Similarly, 3-fold increase ($p < 0.05$) in tumor growth delay and tumor volume DT was observed in SKOV-3TR model. Body weight changes and blood cells counts were used as measures of safety and, except for an increase in platelet counts ($p < 0.05$) in PTX + CER treated animals, there was no difference between various treatment strategies. The results of this study show that combination of PTX and CER in biodegradable polymeric nanoparticles can serve as a very effective therapeutic strategy to overcome drug resistance in ovarian cancer .

OS.CITING REF COUNT: 11 THERE ARE 11 CAPLUS RECORDS THAT CITE THIS RECORD (11 CITINGS)
REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 6 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2007:539325 CAPLUS
DOCUMENT NUMBER: 147:157698
TITLE: Modulation of intracellular ceramide using polymeric nanoparticles to overcome multidrug resistance in cancer
AUTHOR(S): van Vlerken, Lilian E.; Duan, Zhenfeng; Seiden, Michael V.; Amiji, Mansoor M.
CORPORATE SOURCE: Department of Pharmaceutical Sciences, School of Pharmacy, Department of Hematology and Oncology, Massachusetts General Hospital, Northeastern University, Boston, MA, USA
SOURCE: Cancer Research (2007), 67(10), 4843-4850
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal

LANGUAGE: English

AB Although multidrug resistance (MDR) is known to develop through a variety of mol. mechanisms within the tumor cell, many tend to converge toward the alteration of apoptotic signaling. The enzyme glucosylceramide synthase (GCS), responsible for bioactivation of the proapoptotic mediator ceramide to a nonfunctional moiety glucosylceramide, is overexpressed in many MDR tumor types and has been implicated in cell survival in the presence of chemotherapy. The purpose of this study was to investigate the therapeutic strategy of coadministering ceramide with paclitaxel, a commonly used chemotherapeutic agent, in an attempt to restore apoptotic signaling and overcome MDR in the human ovarian cancer cell line SKOV3. Poly(ethylene oxide)-modified poly(epsilon-caprolactone) (PEO-PCL) nanoparticles were used to encapsulate and deliver the therapeutic agents for enhanced efficacy. Results show that indeed the cotherapy eradicates the complete population of MDR cancer cells when they are treated at their IC50 dose of paclitaxel. More interestingly, when the cotherapy was combined with the properties of nanoparticle drug delivery, the MDR cells can be resensitized to a dose of paclitaxel near the IC50 of non-MDR (drug sensitive) cells, indicating a 100-fold increase in chemosensitization via this approach. Mol. anal. of activity verified the hypothesis that the efficacy of this therapeutic approach is indeed due to a restoration in apoptotic signaling, although the beneficial properties of PEO-PCL nanoparticle delivery seemed to enhance the therapeutic success even further, showing the promising potential for the clin. use of this therapeutic strategy to overcome MDR.

OS.CITING REF COUNT: 22 THERE ARE 22 CAPLUS RECORDS THAT CITE THIS RECORD (23 CITINGS)

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 7 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2006:1204388 CAPLUS

DOCUMENT NUMBER: 145:511655

TITLE: Nanoparticulate delivery systems comprising ceramide for treating multi-drug resistance

INVENTOR(S): Amiji, Mansoor M.; Shenoy, Dinesh B.; Vlerken, Lilian Van

PATENT ASSIGNEE(S): Northeastern University, USA

SOURCE: U.S. Pat. Appl. Publ., 11 pp.
CODEN: USXXCO

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 20060257493	A1	20061116	US 2006-413067	20060427
PRIORITY APPLN. INFO.:			US 2005-675837P P	20050428

AB An encapsulated delivery system, and, in particular, a nanoparticulate delivery system representing a qual. different approach to overcoming multi-drug resistance while simultaneously administering the chosen drug treatment to a patient, e.g., in a site-specific manner, is disclosed. A composition according to the invention includes a therapeutically effective amount of one or more multi-drug resistance reversing agents selected from the group consisting of ceramide and ceramide modulators; and a therapeutically effective amount of a therapeutic agent, wherein the therapeutic agent is different from the one or more multi-drug resistance reversing agents, and the one or more multi-drug resistance reversing agents and the therapeutic agent are encapsulated, preferably co-encapsulated, in a biocompatible, biodegradable delivery vehicle for

delivery to a patient in need of treatment, for example, for specific localization at, or higher probability of delivery to, a treatment site in a patient administered the composition Preferably, the one or more multi-drug resistance reversing agents are ceramide, paclitaxel or tamoxifen. Thus, C6-ceramide (CER) and paclitaxel (PAX) were co-encapsulated in poly(ethylene oxide) (PEO)-modified poly(ε-caprolactone) (PCL) nanoparticles. Enhanced apoptotic activity and cell death were observed in vitro in the wildtype human ovarian cancer cell line SKOV3 due to an additive effect of individual PTX and CER cytotoxicities. However, in the multi-drug resistant (MDR) cells, there was significant enhancement of cell death when combining concns. of PTX and CER that individually did not result in significant cell killing.

L5 ANSWER 8 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2006:264352 CAPLUS
DOCUMENT NUMBER: 144:305123
TITLE: Combinations of ceramide and chemotherapeutic agents for inducing tumor cell death
INVENTOR(S): Wanebo, Harold J.; Mehta, Shashikant
PATENT ASSIGNEE(S): Roger Williams Hospital, USA
SOURCE: U.S., 43 pp., Cont.-in-part of U.S. Ser. No. 287,884, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 7015251	B1	20060321	US 2002-958453	20020424
WO 2000059517	A1	20001012	WO 2000-US9440	20000407
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 2020237	A2	20090204	EP 2008-169215	20000407
EP 2020237	A3	20090211		
R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				

PRIORITY APPLN. INFO.: US 1999-287884 B2 19990407
WO 2000-US9440 W 20000407
EP 2000-923188 A3 20000407

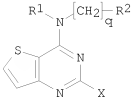
AB This invention provides a method for increasing apoptosis in tumor cells and a method of decreasing a size of a tumor, said methods comprising contacting the tumor cells with: a) an effective amount of at least one antitumor chemotherapeutic agent and b) an effective amount of a ceramide, sequentially or concomitantly, wherein the apoptosis induced by the combination of the antitumor chemotherapeutic agent and the ceramide is greater than the apoptosis induced by contact of the tumor cells with either the antitumor chemotherapeutic agent alone or the ceramide alone. This invention also provides a method of treating cancer in a subject which comprises a method according to either of the above-described methods. This invention provides a method for treating cancer in a subject comprising administering to the subject an effective amount of at least one antitumor chemotherapeutic agent and an effective amount of at least one ceramide, sequentially or

concomitantly. This invention provides a pharmaceutical composition comprising at least one antitumor chemotherapeutic agent in an amount effective to induce apoptosis of tumor cells and at least one ceramide in an amount effective to induce apoptosis of tumor cells and a pharmaceutically acceptable carrier.
REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 9 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2003:532671 CAPLUS
DOCUMENT NUMBER: 139:101145
TITLE: Preparation of thienopyrimidines as inhibitors of prolylpeptidase, inducers of apoptosis and cancer treatment agents
INVENTOR(S): Dumas, Jacques; Sibley, Robert; Wood, Jill
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055890	A1	20030710	WO 2002-US41168	20021220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002364211	A1	20030715	AU 2002-364211	20021220
PRIORITY APPLN. INFO.:			US 2001-343048P P	20011221
			WO 2002-US41168 W	20021220

OTHER SOURCE(S): MARPAT 139:101145
GI



AB The title compds. [I; X = OR3, NR3R4; R1 = H, alkyl; R2 = (un)substituted cycloalkyl, Ph, (un)saturated 4-8 membered heterocyclyl containing 1-3 heteroatoms selected from O and S; R3 = H, alkyl; R4 = (CH2)mA, (CH2)pOA; A = (un)substituted cycloalkyl, (un)saturated 4-8 membered heterocyclyl containing 1-4 heteroatoms selected from N, O and S, etc.; or NR3R4 = (un)saturated 4-8

membered heterocyclyl containing 0-4 heteroatoms selected from N, O and S; m, p = 0-5; q = 0-1; q + (m or p) = 1-6], useful for the inhibiting the prolylpeptidase, inducing apoptosis and treating cancer, were prepared E.g., a 3-step synthesis of I [X = (2-thienylmethyl)amino; R1 = H; R2 = 4-(MeO2C)C6H4; q = 1], starting with thieno[3,2-d]pyrimidine-2,4-diol, was given. All exemplified compds. I were found to inhibit prolylpeptidase at or below of 10 μM.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 10 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2003:532653 CAPLUS

DOCUMENT NUMBER: 139:101144

TITLE: Preparation of quinazolines and quinolines as inhibitors of prolylpeptidase, inducers of apoptosis and cancer treatment agents

INVENTOR(S): Dumas, Jacques; Sibley, Robert; Smith, Roger; Su, Ning; Chen, Yuanwei; Wood, Jill; Guernon, Leatte; Dixon, Julie; Brennan, Catherine; Boyer, Stephen

PATENT ASSIGNEE(S): Bayer Corporation, USA; et al.

SOURCE: PCT Int. Appl., 266 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

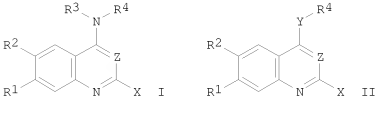
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055866	A1	20030710	WO 2002-US41176	20021220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002361846	A1	20030715	AU 2002-361846	20021220
PRIORITY APPLN. INFO.:			US 2001-343112P	P 20011221
			WO 2002-US41176	W 20021220

OTHER SOURCE(S): MARPAT 139:101144

GI



AB The title compds. [I or II; Z = CH, N; Y = O, S; X = OR5, NR5R6; R1, R2 =

H, NH2, CN, halo, OH, NO2 (wherein R1 and R2 are both not H); R3 = H, alkyl; R4 = (CH2)yR41 (R41 = (un)substituted alkyl; y = 0-2)], useful for the inhibiting the prolyl peptidase, inducing apoptosis and treating cancer, were prepared Thus, reacting 2,4,6-trichloroquinazoline (preparation given) with Me 4-(aminomethyl)benzoate.HCl in the presence of AcONa in H2O followed by treating the resulting Me 4-{[(2,6-dichloro-4-quinazolinyl)amino]methyl}benzoate with piperidine afforded I [Z = N; X = piperidino; R1 = H; R2 = Cl; R3 = H; R4 = 4-(MeO2C)C6H4CH2]. Most of the exemplified compds. I and II were found to inhibit prolylpeptidase at or below of 10 μM.

OS.CITING REF COUNT: 3 THERE ARE 3 CAPLUS RECORDS THAT CITE THIS RECORD (3 CITINGS)

REFERENCE COUNT: 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 11 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2003:532524 CAPLUS

DOCUMENT NUMBER: 139:101141

TITLE: Preparation of 2,4-diaminopyrimidines as inhibitors of prolylpeptidase, inducers of apoptosis and cancer treatment agents

INVENTOR(S): Dumas, Jacques; Dixon, Julie; Sibley, Robert; Wood, Jill

PATENT ASSIGNEE(S): Bayer Corporation, USA

SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

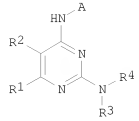
FAMILY ACC. NUM. COUNT: 1

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003055489	A1	20030710	WO 2002-US41146	20021220
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2002367172	A1	20030715	AU 2002-367172	20021220
PRIORITY APPLN. INFO.:			US 2001-343047P	P 20011221
			WO 2002-US41146	W 20021220

OTHER SOURCE(S): MARPAT 139:101141

GI



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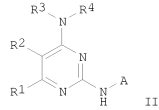

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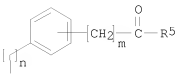
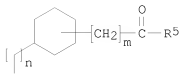


III



IV

AB The title compds. [I or II; R1, R2 = H, halo, OH, etc.; R3 = H; R4 = (un)substituted alkyl, cycloalkyl, aryl, alkylaryl; or NR3R4 = (un)saturated 4-8 membered heterocyclyl which optionally contains 1-3 addnl. heteroatoms selected from N, O and S; A = III or IV; R5 = OH, OR6, NR8R9; R6 = alkyl, haloalkyl, aryl, haloaryl; R8, R9 = H, alkyl, aryl, etc.; n, m = 0-1], useful for the inhibiting prolylpeptidase, inducing apoptosis and treating cancer, were prepared E.g., a 3-step synthesis of I [A = 4-(HO2C)C6H4CH2; R1 = H; R2 = Me; R3 = H; R4 = 2-thienylmethyl], starting from Me 4-(aminomethyl)benzoate and 2,4-dichloro-5-methylpyrimidine, was given. All exemplified compds. I were found to inhibit prolylpeptidase at or below of 10 μM.

OS.CITING REF COUNT: 2 THERE ARE 2 CAPLUS RECORDS THAT CITE THIS RECORD (2 CITINGS)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 12 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN

ACCESSION NUMBER: 2002:963204 CAPLUS

DOCUMENT NUMBER: 138:362308

TITLE: The role of MAPK pathways in the action of chemotherapeutic drugs

AUTHOR(S): Boldt, Simone; Weidle, Ulrich H.; Kolch, Walter

CORPORATE SOURCE: The Beatson Institute for Cancer Research, Cancer Research UK, Glasgow, G61 1BD, UK

SOURCE: Carcinogenesis (2002), 23(11), 1831-1838
CODEN: CRNGDP; ISSN: 0143-3334

PUBLISHER: Oxford University Press

DOCUMENT TYPE: Journal

LANGUAGE: English

AB In this study we have investigated the role of mitogen-induced and stress-activated MAP kinase pathways in the cellular response to taxol, etoposide and ceramide in three different human cancer cell lines: HeLa cervical carcinoma, MCF7 breast cancer and A431 squamous carcinoma cells. The mitogen-induced ERK MAPKs were linked to cell proliferation and survival, whereas the stress-activated MAPKs, p38 and JNK, were connected with apoptosis. Our results show that all drugs activated MAPKs, but that the extent and kinetics of activation were different. In order to assay the biol. consequences of drug-induced MAPK activation we employed selective MAPK inhibitors and measured both long-term clonogenic survival as well as

short-term parameters including apoptosis, mitochondrial metabolic integrity and cell cycle progression. Our results show that drug induced toxicity is not correlated with any singular parameter, but rather a combination of effects on cell cycle and apoptosis. In certain constellations the modulation of MAPK pathways could enhance or decrease drug efficacies. These effects mainly pertained to the regulation of apoptosis and clonogenic survival, but they were highly dependent on the combination of drug and cell line without any clear patterns of correlations emerging. These results suggest that the modulation of MAPK pathways to enhance the efficacy of chemotherapeutic drugs is of limited value unless it is tailored to the specific combination of drug and cancer.

OS.CITING REF COUNT: 65 THERE ARE 65 CAPLUS RECORDS THAT CITE THIS RECORD (66 CITINGS)
REFERENCE COUNT: 62 THERE ARE 62 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 13 OF 13 CAPLUS COPYRIGHT 2009 ACS on STN
ACCESSION NUMBER: 2000:725478 CAPLUS
DOCUMENT NUMBER: 133:276331
TITLE: Ceramide and chemotherapeutic agents for inducing cell death in tumor cells
INVENTOR(S): Wanebo, Harold J.; Mehta, Shashikant
PATENT ASSIGNEE(S): Roger Williams Hospital, USA
SOURCE: PCT Int. Appl., 104 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059517	A1	20001012	WO 2000-US9440	20000407
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1206270	A1	20020522	EP 2000-923188	20000407
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EP 2020237	A2	20090204	EP 2008-169215	20000407
EP 2020237	A3	20090211		
R: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
US 7015251	B1	20060321	US 2002-958453	20020424
PRIORITY APPLN. INFO.:			US 1999-287884	A2 19990407
			EP 2000-923188	A3 20000407
			WO 2000-US9440	W 20000407

AB This invention provides a method for increasing apoptosis in tumor cells and a method of decreasing a size of a tumor, said methods comprising contacting the tumor cells with: (a) an effective amount of at least one antitumor chemotherapeutic agent; and (b) an effective amount of a ceramide, sequentially or concomitantly, wherein the apoptosis induced by the combination of the antitumor chemotherapeutic agent and the ceramide is greater than the apoptosis induced by contact of the tumor cells with either the antitumor chemotherapeutic agent alone or the ceramide alone.

This invention also provides a method of treating cancer in a subject which comprises a method according to either of the above-described methods. This invention provides a method for treating cancer in a subject comprising administering to the subject an effective amount of at least one antitumor chemotherapeutic agent and an effective amount of at least one ceramide, sequentially or concomitantly. This invention provides a pharmaceutical composition comprising at least one antitumor chemotherapeutic agent in an amount effective to induce apoptosis of tumor cells and at least one ceramide in an amount effective to induce apoptosis of tumor cells and a pharmaceutically acceptable carrier. Paclitaxel-induced apoptosis in Jurkat cells was enhanced by C6-N-hexanoyl-D-sphingosine.

OS.CITING REF COUNT: 5 THERE ARE 5 CAPLUS RECORDS THAT CITE THIS RECORD (5 CITINGS)

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

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FILE 'REGISTRY' ENTERED AT 15:58:30 ON 17 AUG 2009
L1 1 S C6-CERAMIDE/CN

FILE 'CAPLUS' ENTERED AT 15:58:44 ON 17 AUG 2009
L2 252 S L1
L3 85 S L2 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM?)
L4 3 S L3 AND AD<19990407
L5 13 S L3 AND (PACLITAXEL OR TAXOL)

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FULL ESTIMATED COST	67.68	75.78

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-13.12	-13.12

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FILE 'BIOSIS' ENTERED AT 16:03:15 ON 17 AUG 2009
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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	3.21	78.99

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CA SUBSCRIBER PRICE	0.00	-13.12

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                                                         ENTRY    SESSION
FULL ESTIMATED COST                                      15.08      94.07

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
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S L6
L7         596 L6

=> s l7 and (?cancer? or ?tumor? or ?tumour? or ?neoplasm?)
L8         239 L7 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM?)

=> dup rem l8
PROCESSING COMPLETED FOR L8
L9          144 DUP REM L8 (95 DUPLICATES REMOVED)

=> s l9 and (pd<19990407 or py<2000 or prd<19990407)
'19990407' NOT A VALID FIELD CODE
   1 FILES SEARCHED...
'19990407' NOT A VALID FIELD CODE
'19990407' NOT A VALID FIELD CODE
L10         44 L9 AND (PD<19990407 OR PY<2000 OR PRD<19990407)

=> s l10 and (paclitaxel or taxol)
L11          0 L10 AND (PACLITAXEL OR TAXOL)

=> d l10 1-44 ibib abs

L10  ANSWER 1 OF 44     MEDLINE on STN
ACCESSION NUMBER:   2000040630     MEDLINE
DOCUMENT NUMBER:    PubMed ID: 10570152
TITLE:              Stimulation of CD95 (Fas) blocks T lymphocyte calcium
                    channels through sphingomyelinase and sphingolipids.
AUTHOR:             Lepple-Wienhues A; Belka C; Laun T; Jekle A; Walter B;
                    Wieland U; Welz M; Heil L; Kun J; Busch G; Weller M;
                    Bamberg M; Gulbins E; Lang F
```

CORPORATE SOURCE: Department of Physiology I, University of Tubingen, Gmelinstr. 5, D-72076 Tubingen, Germany.. alepplew@uni-tuebingen.de
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1999 Nov 23) Vol. 96, No. 24, pp. 13795-800.
Journal code: 7505876. ISSN: 0027-8424.
Report No.: NLM-PMC24144.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200001
ENTRY DATE: Entered STN: 14 Jan 2000
Last Updated on STN: 14 Jan 2000
Entered Medline: 6 Jan 2000

AB Calcium influx through store-operated calcium release-activated calcium channels (CRAC) is required for T cell activation, cytokine synthesis, and proliferation. The CD95 (Apo-1/Fas) receptor plays a role in self-tolerance and tumor immune escape, and it mediates apoptosis in activated T cells. In this paper we show that CD95-stimulation blocks CRAC and Ca(2+) influx in lymphocytes through the activation of acidic sphingomyelinase (ASM) and ceramide release. The block of Ca(2+) entry is lacking in CD95-defective lpr lymphocytes as well as in ASM-defective cells and can be restored by retransfection of ASM. C2 ceramide, C6 ceramide, and sphingosine block CRAC reversibly, whereas the inactive dihydroceramide has no effect. CD95-stimulation or the addition of ceramide prevents store-operated Ca(2+) influx, activation of the transcriptional regulator NFAT, and IL-2 synthesis. The block of CRAC by sphingomyelinase metabolites adds a function to the repertoire of the CD95 receptor inhibiting T cell activation signals.

L10 ANSWER 2 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999357914 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10427137
TITLE: Modification of ceramide metabolism increases cancer cell sensitivity to cytotoxics.
AUTHOR: Lucci A; Han T Y; Liu Y Y; Giuliano A E; Cabot M C
CORPORATE SOURCE: John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA 90404, USA.
CONTRACT NUMBER: CA77632 (United States NCI NIH HHS)
SOURCE: International journal of oncology, (1999 Sep) Vol. 15, No. 3, pp. 541-6.
Journal code: 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 26 Oct 1999
Last Updated on STN: 26 Oct 1999
Entered Medline: 14 Oct 1999

AB In the preceding report we demonstrated that MCF-7-AdrR cells (adriamycin resistant) were insensitive to ceramide, whereas MCF-7 wild-type cells were sensitive. It was also shown that the drug resistant cells had an increased capacity to convert ceramide to glucosylceramide. Here we demonstrate that blocking the conversion of ceramide to glucosylceramide increases MCF-7-AdrR cell sensitivity to ceramide as well as to

antitumor agents. Treatment of MCF-7 cells with adriamycin elicited a 5-fold increase in ceramide, and caused oligonucleosomal fragmentation, characteristic to apoptosis. Under similar treatment conditions, ceramide was not generated in MCF-7-AdrR cells. In MCF-7-AdrR cells neither C6-ceramide nor tamoxifen was cytotoxic; however, the addition of tamoxifen to the C6-ceramide treatment regimen reduced cell viability to 42% and elicited apoptosis. Treatment of MCF-7-AdrR cells with Adriamycin promoted an increase in ceramide only if tamoxifen was present, in which case ceramide increased 7-fold, and cell viability decreased to 50%. The employment of another agent, RU486 (Mifepristone), which blocks ceramide glycosylation, increased MCF-7-AdrR cell sensitivity to adriamycin in a dose-dependent manner. Our data show that agents that block ceramide glycosylation potentiate cellular sensitivity to ceramide and to chemotherapeutic drugs, and suggest that the ceramide metabolic pathway is an important target for anticancer drug development.

L10 ANSWER 3 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999357913 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10427136
TITLE: Ceramide toxicity and metabolism differ in wild-type and multidrug-resistant cancer cells.
AUTHOR: Lucci A; Giuliano A E; Han T Y; Dinur T; Liu Y Y; Senchenkov A; Cabot M C
CORPORATE SOURCE: John Wayne Cancer Institute at Saint John's Health Center, Santa Monica, CA 90404, USA.
CONTRACT NUMBER: CA77362 (United States NCI NIH HHS)
SOURCE: International journal of oncology, (1999 Sep) Vol. 15, No. 3, pp. 535-40. Journal code: 9306042. ISSN: 1019-6439.
PUB. COUNTRY: Greece
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199910
ENTRY DATE: Entered STN: 26 Oct 1999 Last Updated on STN: 26 Oct 1999 Entered Medline: 14 Oct 1999

AB Previously we demonstrated that multidrug-resistant (MDR) cancer cells have elevated levels of a glycosylated form of ceramide, glucosylceramide. Here we compared ceramide metabolism and ceramide toxicity in MCF-7 and in adriamycin-resistant (MCF-7-AdrR) human breast cancer cells. MCF-7-AdrR cells were resistant to C6-ceramide (1-10 microM); however, in MCF-7 cells treated with C6-ceramide, viability dropped sharply. Ceramide, when supplemented, was not metabolized by MCF-7 cells. In contrast, ceramide was efficiently converted to glucosylceramide by MCF-7-AdrR cells. Analysis of extracellular [3H]ceramide in radiolabeled cells showed that MCF-7-AdrR cells do not have an enhanced capacity to efflux ceramide compared with MCF-7 cells. Triphenylethylene anti-estrogens, known modulators of drug resistance, were effective inhibitors of ceramide conversion to glucosylceramide, suggesting that blocking ceramide metabolism plays a role in chemosensitization. The anti-progestine, RU486, also blocked glucosylceramide synthesis in cells; however, LY117018, a raloxifene analog, was without influence. We propose that an enhanced capacity to glycosylate ceramide as evidenced in MCF-7-AdrR cells, is a molecular determinant of drug resistance, particularly as regards resistance to ceramide-enhancing agents such as anthracyclines, ionizing radiation, and tumor necrosis factor-alpha.

L10 ANSWER 4 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999345468 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10419100
TITLE: Tumor necrosis factor-alpha and ceramides in insulin resistance.
AUTHOR: Brindley D N; Wang C N; Mei J; Xu J; Hanna A N
CORPORATE SOURCE: Department of Biochemistry (Signal Transduction Laboratories), University of Alberta, Edmonton, Canada.. david.brindley@ualberta.ca
SOURCE: Lipids, (1999) Vol. 34 Suppl, pp. S85-8. Journal code: 0060450. ISSN: 0024-4201.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199909
ENTRY DATE: Entered STN: 21 Sep 1999
Last Updated on STN: 21 Sep 1999
Entered Medline: 8 Sep 1999

AB The present studies tested the hypothesis that some effects of tumor necrosis factor-alpha (TNF-alpha) are mediated by activation of sphingomyelinases and the production of ceramides. Differentiated 3T3-L1 adipocytes were incubated with short-chain ceramide analogs, (C2- and C6-ceramides: N-acetyl- and N-hexanoyl-sphingosines, respectively), and this treatment increased 2-deoxyglucose uptake in the absence of insulin progressively from 2-24 h. This effect was inhibited by blocking the activations of mitogen-activated protein kinase, phosphatidylinositol 3-kinase (PI 3-kinase), and ribosomal S6 kinase which mediated an increase in GLUT1 concentrations. Long-term increases in PI 3-kinase activity associated with insulin receptor substrate-1 (IRS-1) increased the proportion of GLUT1 and GLUT4 in plasma membranes. These events explain the increases in noninsulin-dependent glucose uptake and incorporation of this glucose into the fatty acid and glycerol moieties of triacylglycerol. The mechanisms by which TNF-alpha and ceramides increase PI 3-kinase activity were investigated further by using rat2 fibroblasts. Incubation for 20 min with TNF-alpha, bacterial sphingomyelinase, or C2-ceramides increased PI 3-kinase activity by about fivefold, and this effect depended upon a stimulation of tyrosine kinase activity and an increase in Ras-GTP. This demonstrates the existence of a novel signaling pathway for TNF-alpha that could contribute to the effects of this cytokine in stimulating basal glucose uptake. By contrast, treating the 3T3-L1 adipocytes for 2-24 h with C2-ceramide diminished insulin-stimulated glucose uptake by decreasing the insulin-induced translocation of GLUT1 and GLUT4 to plasma membranes. This inhibition was observed when there was no increase in basal glucose uptake, and it occurred downstream of PI 3-kinase. Our work provides further mechanisms whereby TNF-alpha and ceramides produce insulin resistance and decrease the effectiveness of insulin in stimulating glucose disposal from the blood. Conversely, TNF-alpha and ceramides increase the ability of adipocytes to take up glucose and store triacylglycerol in the absence of insulin.

L10 ANSWER 5 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999316703 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10389841
TITLE: Activation of the sphingomyelinase/ceramide signal transduction pathway in insulin-secreting beta-cells: role in cytokine-induced beta-cell death.
AUTHOR: Major C D; Gao Z Y; Wolf B A
CORPORATE SOURCE: Department of Pathology and Laboratory Medicine, University of Pennsylvania School of Medicine, Philadelphia

19104-6082, USA.
CONTRACT NUMBER: DK-43354 (United States NIDDK NIH HHS)
DK-49814 (United States NIDDK NIH HHS)
K04 DK-02217 (United States NIDDK NIH HHS)
+
SOURCE: Diabetes, (1999 Jul) Vol. 48, No. 7, pp. 1372-80.
Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199907
ENTRY DATE: Entered STN: 30 Jul 1999
Last Updated on STN: 30 Jul 1999
Entered Medline: 22 Jul 1999

AB Activation of the sphingomyelin/ceramide pathway may mediate interleukin-1-induced beta-cell death (Welsh, N: Interleuken-1beta-induced ceramide and diacylglycerol generation may lead to activation of the c-Jun NH2-terminal kinase and the transcription factor ATF-2 in the insulin-producing cell line RINm5F. J Biol Chem 271: 8307-8312, 1996). In this report, we have examined this pathway in more detail. Culture of beta-TC3 cells with 25 micromol/l ceramide analogs (N-acetyl- and N-hexanoylsphingosine) for 72 h did not significantly affect glucose- and carbachol-induced insulin secretion. Dihydroceramide (N-acetyl- or N-hexanoylsphinganine), a structurally similar analog, had no effect on agonist-induced secretion. However, ceramide analogs both time- and dose-dependently decreased cell viability, while the dihydroceramide analog had no effect. The ceramide effect on cell viability mimicked the effect of the cytokines TNF-alpha, IL-1beta, and IFN-gamma, reported stimulators of sphingomyelin hydrolysis. Cytokines, however, failed to stimulate sphingomyelin metabolism. Furthermore, using two different methods to quantitate ceramide, cytokines failed to cause an increase in beta-cell ceramide content versus unstimulated or time-matched vehicle controls. Taken together, these data suggest that although ceramide analogs mimic the cytotoxic effect of cytokines, activation of the sphingomyelin/ceramide signaling pathway is not involved in cytokine-induced beta-cell death.

L10 ANSWER 6 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999314729 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10454830
TITLE: Macrophage TNF mRNA expression induced by LPS is regulated by sphingomyelin metabolites.
AUTHOR: Lo C J; Fu M; Lo F R; Cryer H G
CORPORATE SOURCE: Department of Surgery, University of California, Los Angeles 90095-6904, USA.. clo@surgery.medsch.ucla.edu
SOURCE: Shock (Augusta, Ga.), (1999 Jun) Vol. 11, No. 6, pp. 411-5.
Journal code: 9421564. ISSN: 1073-2322.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199908
ENTRY DATE: Entered STN: 27 Aug 1999
Last Updated on STN: 27 Aug 1999
Entered Medline: 17 Aug 1999

AB Metabolism of macrophage (MO) membrane phospholipids produces key mediators of inflammation and major second messengers that modulate inflammatory responses during sepsis. Sphingomyelin is a major class of

phospholipid that releases ceramide and sphingosine. This study was designed to investigate the involvement of sphingomyelin metabolites in MO activation by lipopolysaccharide (LPS). Rabbit alveolar MO were obtained by bronchoalveolar lavage and exposed to C6-ceramide, a cell-permeable analogue of natural ceramide, or sphingosine in the presence of Escherichia coli LPS (100 ng/mL). Tumor necrosis factor (TNF) mRNA expression was measured by Northern blot assays. Total nuclear extract was harvested for the measurement of nuclear factor KB (NFkappaB) with electrophoretic mobility shift assays. MO TNF production was measured by L929 bioassays. C-6 ceramide did not have any effects on MO TNF production or TNF mRNA expression with or without LPS stimulation. Inhibition of ceramide metabolism with 1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP), or N-oleoyl-ethanolamine (NOE) also did not induce TNF mRNA or TNF production. In comparison, sphingosine inhibited TNF mRNA expression as well as TNF production of LPS-stimulated MO. LPS-induced MO NFkappaB activity was also reduced by sphingosine. Our data indicate that ceramide alone has no effect on macrophage activity, but its metabolite sphingosine down-regulates MO activation induced by LPS stimulation. Therefore, the sphingomyelin pathway is involved in the regulation of MO activation.

L10 ANSWER 7 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999240763 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10224136
TITLE: Apoptosis-inducing agents cause rapid shedding of tumor necrosis factor receptor 1 (TNFR1). A nonpharmacological explanation for inhibition of TNF-mediated activation.
AUTHOR: Madge L A; Sierra-Honigmann M R; Pober J S
CORPORATE SOURCE: Molecular Cardiobiology Program, Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, Connecticut 06536-0812, USA.
CONTRACT NUMBER: HL-36007 (United States NHLBI NIH HHS)
SOURCE: The Journal of biological chemistry, (1999 May 7) Vol. 274, No. 19, pp. 13643-9. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199906
ENTRY DATE: Entered STN: 14 Jun 1999 Last Updated on STN: 19 Sep 2002 Entered Medline: 3 Jun 1999

AB Several chemical compounds not known to interact with tumor necrosis factor (TNF) signal transduction proteins inhibit TNF-mediated activation of vascular endothelial cells (EC). Four structurally diverse agents, arachidonyl trifluoromethylketone, staurosporine, sodium salicylate, and C6-ceramide, were studied. All four agents caused EC apoptosis at concentrations that inhibited TNF-induced IkappaBalpha degradation. However, evidence of apoptosis was not evident until after several (e.g. 3-12) hours of treatment, whereas 2 h of treatment was sufficient to inhibit TNF responses. IL-1-induced IkappaBalpha degradation was unaffected by these treatments. Inhibition of TNF signaling could not be prevented with either of the broad spectrum caspase inhibitors zVADfmk or yVADcmk. The inhibition of p38 kinase with SB203580 prevented the inhibition of TNF signaling by all agents except arachidonyl trifluoromethylketone. No changes in the levels or molecular weights of the adaptor proteins TRADD (TNF receptor-associated death domain), RIP (receptor-interacting protein), or TRAF2 (TNF

receptor-associated factor-2) were caused by apoptogenic drugs. However, TNF receptor 1 (TNFR1) surface expression was significantly reduced by all four agents. Furthermore, TNF-dependent recruitment of TRADD to surface TNFR1 was also inhibited. These data suggest that several putative inhibitors of TNF signaling work by triggering apoptosis and that an early event coincident with the initiation of apoptosis, preceding evidence of injury, is loss of TNFR1. Consistent with this hypothesis, cotreatment of EC with the metalloproteinase inhibitor Tapi (TNF-alpha proteinase inhibitor) blocked the reduction in surface TNFR1 by apoptogenic drugs and prevented inhibition of TNF-induced IkappaBalpha degradation without blocking apoptosis. TNFR1 loss could be a mechanism to limit inflammation in response to apoptotic cell death.

L10 ANSWER 8 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999218649 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10200538
TITLE: Apoptosis induced by N-hexanoylsphingosine in CHP-100 cells associates with accumulation of endogenous ceramide and is potentiated by inhibition of glucocerebroside synthesis.
AUTHOR: Spinedi A; Bartolomeo S D; Piacentini M
CORPORATE SOURCE: Department of Biology, University of Rome 'Tor Vergata', Via della Ricerca Scientifica, 00133 Rome, Italy.
SOURCE: Cell death and differentiation, (1998 Sep) Vol. 5, No. 9, pp. 785-91.
Journal code: 9437445. ISSN: 1350-9047.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199905
ENTRY DATE: Entered STN: 14 Jun 1999
Last Updated on STN: 14 Jun 1999
Entered Medline: 28 May 1999
AB We report that apoptosis induced by N-hexanoylsphingosine (C6-Cer) in CHP-100 human neuroepithelioma cells associates with accumulation of monohexosylsphingolipids produced not only by short-chain ceramide glycosylation but also through glycosylation of a ceramide pool endogenously produced. By high-performance thin layer chromatography on borate silica gel plates, newly formed monohexosylsphingolipids were identified as glucosylceramides (GluCer); however, accumulation of lactosylceramide or higher-order glycosphingolipids was not observed. GluCer accumulation was fully suppressed by D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol; moreover, while this inhibitor had no effect on cell viability when administered alone, it markedly potentiated the apoptotic effect of C6-Cer. These results provide evidence that activation of GluCer synthesis is an important mechanism through which CHP-100 cells attempt to escape ceramide-induced apoptosis.

L10 ANSWER 9 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999194782 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10092616
TITLE: Tumor necrosis factor-alpha, sphingomyelinase, and ceramide inhibit store-operated calcium entry in thyroid FRTL-5 cells.
AUTHOR: Tornquist K; Malm A M; Pasternack M; Kronqvist R; Bjorklund S; Tuominen R; Slotte J P
CORPORATE SOURCE: Department of Biology, Abo Akademi University, BioCity, 20520 Turku, Finland.. kid.tornqvist@abo.fi
SOURCE: The Journal of biological chemistry, (1999 Apr 2)

Vol. 274, No. 14, pp. 9370-7.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 11 May 1999
Last Updated on STN: 11 May 1999
Entered Medline: 27 Apr 1999

AB Tumor necrosis factor alpha (TNF-alpha) is a potent inhibitor of proliferation in several cell types, including thyroid FRTL-5 cells. As intracellular free calcium ([Ca2+]i) is a major signal in activating proliferation, we investigated the effect of TNF-alpha on calcium fluxes in FRTL-5 cells. TNF-alpha per se did not modulate resting [Ca2+]i. However, preincubation (10 min) of the cells with 1-100 ng/ml TNF-alpha decreased the thapsigargin (Tg)-evoked store-operated calcium entry in a concentration-dependent manner. TNF-alpha did not inhibit the mobilization of sequestered calcium. To investigate whether the effect of TNF-alpha on calcium entry was mediated via the sphingomyelinase pathway, the cells were pretreated with sphingomyelinase (SMase) prior to stimulation with Tg. SMase inhibited the Tg-evoked calcium entry in a concentration-dependent manner. Furthermore, an inhibition of calcium entry was obtained after preincubation of the cells with the membrane-permeable C2-ceramide and C6-ceramide analogues. The inactive ceramides dihydro-C2 and dihydro-C6 showed only marginal effects. Neither SMase, C2-ceramide, nor C6-ceramide affected the release of sequestered calcium. C2- and C6-ceramide also decreased the ATP-evoked calcium entry, without affecting the release of sequestered calcium. The effect of TNF-alpha and SMase was inhibited by the kinase inhibitor staurosporin and by the protein kinase C (PKC) inhibitor calphostin C but not by down-regulation of PKC. However, we were unable to measure a significant activation of PKC using TNF-alpha or C6-ceramide. The effect of TNF-alpha was not mediated via activation of either c-Jun N-terminal kinase or p38 kinase. We were unable to detect an increase in the ceramide (or sphingosine) content of the cells after stimulation with TNF-alpha for up to 30 min. Thus, one mechanism of action of TNF-alpha, SMase, and ceramide on thyroid FRTL-5 cells is to inhibit calcium entry.

L10 ANSWER 10 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999160885 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10049730
TITLE: N-Oleoylethanolamine inhibits glucosylation of natural ceramides in CHP-100 neuroepithelioma cells: possible implications for apoptosis.
AUTHOR: Spinedi A; Di Bartolomeo S; Piacentini M
CORPORATE SOURCE: Department of Biology, University of Rome 'Tor Vergata', Italy.. spinedi@uniroma2.it
SOURCE: Biochemical and biophysical research communications, (1999 Feb 16) Vol. 255, No. 2, pp. 456-9.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 24 Mar 1999
Last Updated on STN: 3 Mar 2000
Entered Medline: 11 Mar 1999

AB We report that N-oleoylethanolamine (NOE), widely employed as a ceramidase inhibitor, also inhibits glucosylation of naturally occurring ceramides. When CHP-100 neuroepithelioma cells were exposed for 18h to non-toxic NOE concentrations (i.e. up to 70 microM), basal incorporation of labelled hexose into glucosylceramide (GlcCer) and higher order neutral glycosphingolipids was significantly inhibited. In cells treated with 30 microM N-hexanoylsphingosine (C6-Cer), NOE affected only marginally short-chain glucocerebroside accumulation, but markedly decreased accumulation of glucocerebrosides originating from glucosylation of a long-chain ceramide (Lc-Cer) pool produced upon C6-Cer treatment. Evidence is provided that NOE effects neither are mediated by their effects on ceramidase nor are due to enhanced long-chain GlcCer (Lc-GlcCer) conversion to higher order glycosylated derivatives. NOE inhibition of Lc-GlcCer generation was accompanied by enhanced accumulation of Lc-Cer and by potentiation of apoptosis induced by C6-Cer; the possible causal relationships between these two phenomena are discussed.

L10 ANSWER 11 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999138900 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9973477
TITLE: Lysophosphatidic acid and sphingosine 1-phosphate protection of T cells from apoptosis in association with suppression of Bax.
AUTHOR: Goetzl E J; Kong Y; Mei B
CORPORATE SOURCE: Department of Medicine, University of California Medical Center, San Francisco 94143, USA.. egoetzl@itsa.ucsf.edu
CONTRACT NUMBER: HL31809 (United States NHLBI NIH HHS)
SOURCE: Journal of immunology (Baltimore, Md. : 1950), (1999 Feb 15) Vol. 162, No. 4, pp. 2049-56.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199904
ENTRY DATE: Entered STN: 26 Apr 1999
Last Updated on STN: 19 Sep 2002
Entered Medline: 13 Apr 1999

AB Members of a subfamily of G protein-coupled receptors (GPCRs), encoded by five different endothelial differentiation genes (edgs), specifically mediate effects of lysophosphatidic acid (LPA) and sphingosine 1-phosphate (S1P) on cellular proliferation and differentiation. Mechanisms of suppression of apoptosis by LPA and S1P were studied in the Tsup-1 cultured line of human T lymphoblastoma cells, which express Edg-2 and Edg-4 GPCRs for LPA and Edg-3 and Edg-5 GPCRs for S1P. At 10-10 M to 10-7 M, both LPA and S1P protected Tsup-1 cells from apoptosis induced by Abs to Fas, CD2, and CD3 plus CD28 in combination. Apoptosis elicited by C6 ceramide was inhibited by S1P, but not by LPA, in part because ceramide suppressed expression of Edg-2 and Edg-4 surface receptors for LPA without affecting Edg-3 surface receptors for S1P. At 10-9 M to 10-7 M, LPA and S1P significantly suppressed cellular levels of the apoptosis-promoting protein Bax, without altering the levels of Bcl-xL or Bcl-2 assessed by Western blots and immunoassays. Transfections of pairs of antisense plasmids for Edg-2 plus Edg-4 and Edg-3 plus Edg-5, and hygromycin selection of transfectants with reduced expression of the respective Edg R proteins in Western blots, inhibited both protection from apoptosis and reduction in cellular levels of Bax by LPA and S1P. Thus, LPA and S1P protection from apoptosis is mediated by distinct Edg GPCRs and may involve novel effects on Bax regulatory protein.

L10 ANSWER 12 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999112912 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9895291
TITLE: N-Acetylsphingosine stimulates phosphatidylglycerolphosphate synthase activity in H9c2 cardiac cells.
AUTHOR: Xu F Y; Kelly S L; Hatch G M
CORPORATE SOURCE: Department of Pharmacology and Therapeutics, University of Manitoba, 770 Bannatyne Avenue, Winnipeg, Manitoba, Canada R3E OW3.
SOURCE: The Biochemical journal, (1999 Feb 1) Vol. 337 (Pt 3), pp. 483-90.
Journal code: 2984726R. ISSN: 0264-6021.
Report No.: NLM-PMC1219999.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199903
ENTRY DATE: Entered STN: 13 Apr 1999
Last Updated on STN: 13 Apr 1999
Entered Medline: 30 Mar 1999

AB Cardiolipin and phosphatidylglycerol biosynthesis were examined in H9c2 cells incubated with short-chain ceramides. Incubation of cells with N-acetylsphingosine or N-hexanoylsphingosine stimulated [1, 3-3H]glycerol incorporation into phosphatidylglycerol and cardiolipin, with N-acetylsphingosine having the greater effect. The mechanism for the ceramide-mediated stimulation of de novo phosphatidylglycerol and cardiolipin biosynthesis appeared to be an increase in the activity of phosphatidylglycerolphosphate synthase, the committed step of phosphatidylglycerol and cardiolipin biosynthesis. The presence of the potent protein phosphatase inhibitors calyculin A or okadaic acid attenuated the N-acetylsphingosine-mediated stimulation of phosphatidylglycerolphosphate synthase activity and of phosphatidylglycerol and cardiolipin biosynthesis, indicating the involvement of a ceramide-activated protein phosphatase(s). The presence of 8-(4-chlorophenylthio)-cAMP (CPT-cAMP) stimulated enzyme activity and [1,3-3H]glycerol incorporation into phosphatidylglycerol and cardiolipin. The effects of CPT-cAMP and N-acetylsphingosine on phosphatidylglycerol and cardiolipin biosynthesis and on phosphatidylglycerolphosphate synthase activity were additive. Phosphatidylglycerol biosynthesis from sn-[14C]glycerol 3-phosphate in permeabilized H9c2 cells was stimulated by preincubation with N-acetylsphingosine, and this was attenuated by okadaic acid. N-Acetylsphingosine treatment of cells elevated mitochondrial phospholipase A2 activity. Since the pool sizes of phosphatidylglycerol and cardiolipin were unaltered in these cells, the observed increase in phosphatidylglycerolphosphate synthase activity may be a compensatory mechanism for the N-acetylsphingosine-mediated elevation of mitochondrial phospholipase A2 activity. Finally, addition of tumour necrosis factor alpha to H9c2 cells resulted in an elevation of both phosphatidylglycerolphosphate synthase and phospholipase A2 activities. The results suggest that phosphatidylglycerol and cardiolipin metabolism in H9c2 cells may be regulated by intracellular ceramide signalling.

L10 ANSWER 13 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999023203 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9808050
TITLE: Analysis of bax protein in sphingosine-induced apoptosis in the human leukemic cell line TF1 and its bcl-2 transfectants.

AUTHOR: Isogai C; Murate T; Tamiya-Koizumi K; Yoshida S; Ito T; Nagai H; Kinoshita T; Kagami Y; Hotta T; Hamaguchi M; Saito H
CORPORATE SOURCE: First Department of Internal Medicine, Nagoya University School of Medicine, Japan.
SOURCE: Experimental hematology, (1998 Nov) Vol. 26, No. 12, pp. 1118-25.
Journal code: 0402313. ISSN: 0301-472X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199811
ENTRY DATE: Entered STN: 6 Jan 1999
Last Updated on STN: 6 Jan 1999
Entered Medline: 19 Nov 1998

AB Sphingosine, a sphingolipid breakdown product, has been proposed as an apoptosis-inducing agent. In this study, we examined the effect of sphingosine in bcl-2-overexpressing cells compared with cells that do not express the bcl-2 gene. The human erythroleukemic cell line TF1, which lacks bcl-2 expression, was easily induced to undergo apoptotic cell death by a variety of stimuli, including depletion of granulocyte-macrophage colony-stimulating factor (GM-CSF) or exposure to methylmethane sulfonate (MMS) (100 microg/mL), ultraviolet light (15 J/m2), X-ray irradiation (20 Gy), or sphingosine, a sphingolipid breakdown product (5 microM). In contrast, bcl-2 transfectants of TF1 (TF1-bcl2), which we established, were resistant to most of these treatments but remained sensitive to sphingosine. Neither C2- nor C6-ceramide (short-chain ceramide) induced apoptosis in TF1-mock and TF1-bcl2 cells. Sphingosine-induced apoptosis could not be inhibited by fumonisin B1, which can prevent conversion of sphingosine to ceramide, suggesting that sphingosine itself, not ceramide, possesses apoptosis-inducing capability. Western blotting, which revealed a 21-kDa bax protein in untreated cells, revealed the presence of an additional 18-kDa protein in GM-CSF-depleted and MMS- or sphingosine-treated TF1-mock cells. In TF1-bcl2 cells, this protein was not detected after GM-CSF depletion or MMS treatment, but was observed after sphingosine treatment. Immunoprecipitation with anti-bcl2 antibody, followed by immunoblotting with anti-bax antibody, showed that both the 21-kDa bax protein and the 18-kDa protein heterodimerized with bcl-2 protein. These results suggest that sphingosine is a unique reagent for apoptosis and that it can overcome bcl-2 gene expression. Furthermore, induction of 18-kDa bax-related protein may play an important role in apoptosis. Sphingosine, but not ceramide, may prove applicable as a reagent for future cytotoxic drugs used to treat intractable tumors overexpressing bcl-2.

L10 ANSWER 14 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1999018187 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9799530
TITLE: Enzymatic synthesis of omega-amino-ceramide: preparation of a sensitive fluorescent substrate for ceramidase.
AUTHOR: Tani M; Kita K; Komori H; Nakagawa T; Ito M
CORPORATE SOURCE: Faculty of Agriculture, Kyushu University, 6-10-1, Hakozaki, Fukuoka, Higashi-ku, 812-8581, Japan.
SOURCE: Analytical biochemistry, (1998 Oct 15) Vol. 263, No. 2, pp. 183-8.
Journal code: 0370535. ISSN: 0003-2697.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 15 Jan 1999
Last Updated on STN: 15 Jan 1999
Entered Medline: 16 Dec 1998

AB Sphingolipid ceramide N-deacylase catalyzes the reversible reactions in which the N-acyl linkage of ceramides of various sphingolipids is hydrolyzed or synthesized under different conditions. We report here a new method for preparation of ceramide containing omega-amino-fatty acid by using the condensation reaction of the enzyme. omega-Aminododecanoic acids were efficiently condensed by the enzyme to sphingosine in 25 mM glycine-NaOH buffer, pH 10, containing 0.3% Triton X-100 when the amino residue at the omega position of the fatty acid was blocked with trifluoroacetate. The reaction product was purified sequentially from the reaction mixture on a C18 reversed-phase column and Sep-Pak Plus Silica and Sep-Pak QMA cartridges with an overall yield of 80% and determined to be omega-aminododecanoylsphingosine by thin-layer chromatography and fast atom bombardment-mass spectrometry analyses after removing the block of trifluoroacetate by alkaline treatment. The enzyme can also be applied successfully to the synthesis of various glycosphingolipids and sphingomyelin containing omega-aminododecanoic acids. The 7-nitrobenz-2-oxa-1,3-diazole (NBD)-labeled N-dodecanoylsphingosine was easily prepared from the omega-amino-ceramide by coupling with NBD-fluoride. This fluorescent ceramide was found to be hydrolyzed by ceramidase of B16 melanoma cells much faster than NBD-labeled N-hexanoylsphingosine in vitro as well as in vivo, indicating that the former is an excellent substrate for the assay of ceramidase.

L10 ANSWER 15 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1998383969 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9719464
TITLE: Induction of p21 during ceramide-mediated apoptosis in human hepatocarcinoma cells.
AUTHOR: Oh W J; Kim W H; Kang K H; Kim T Y; Kim M Y; Choi K H
CORPORATE SOURCE: Department of Life Science, College of Natural Sciences, Chung-Ang University, Seoul, South Korea.
SOURCE: Cancer letters, (1998 Jul 17) Vol. 129, No. 2, pp. 215-22.
Journal code: 7600053. ISSN: 0304-3835.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY DATE: Entered STN: 17 Sep 1998
Last Updated on STN: 17 Sep 1998
Entered Medline: 8 Sep 1998

AB Ceramide acts as a mediator of programmed cell death in various cell types, but its molecular mechanisms linked to the cell cycle are poorly understood. In this study, we investigated the expression of the p21 gene and its relationship to apoptosis induced by ceramide. In SK-HEP-1 cells, the addition of C6-ceramide resulted in a dose- and time-dependent growth suppression and DNA fragmentation characteristics of apoptosis. p21 protein was induced during that process, while the protein level of p53, known as a transcriptional activator of p21, was not elevated under the same condition. This apoptotic cell death with p21 induction was also observed in the Hep 3B cells lacking functional p53 after exposure to C6-ceramide. These findings suggest that ceramide-induced apoptosis is associated with the upregulation of p21 mRNA and protein in a p53-independent pathway.

L10 ANSWER 16 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1998192689 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9524193
TITLE: 1,25-Dihydroxy vitamin D3 and tri-iodothyronine stimulate the expression of a protein immunologically related to osteocalcin.
AUTHOR: Luegmayr E; Varga F; Glantschnig H; Fratzl-Zelman N; Rumpler M; Ellinger A; Klaushofer K
CORPORATE SOURCE: Ludwig Boltzmann Institute of Osteology, Fourth Medical Department, Hanusch-Hospital, Vienna, Austria.
SOURCE: The journal of histochemistry and cytochemistry : official journal of the Histochemistry Society, (1998 Apr) Vol. 46, No. 4, pp. 477-86.
Journal code: 9815334. ISSN: 0022-1554.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199805
ENTRY DATE: Entered STN: 14 May 1998
Last Updated on STN: 14 May 1998
Entered Medline: 6 May 1998

AB Osteocalcin (OC), a bone-specific protein, is a marker of late osteoblastic differentiation. Its expression is influenced by various growth factors and hormones. We investigated the effect of 1, 25-dihydroxy vitamin D3 (D3) and tri-iodothyronine (T3) on OC expression in osteoblast-like MC3T3-E1 cells. A heterologous OC green fluorescence protein (GFP) fusion vector was established and expressed to study possible effects on protein transport. Immunostaining of endogenous OC revealed a significant increase in the percentage of positive cells after D3 and T3 treatment. This was consistent for MC3T3-E1 cells as well as nonosteogenic NIH-3T3 and mammary carcinoma cells, but not for neuroblastoma cells. The perinuclear immunostaining corresponded to the NBD C6 ceramide Golgi staining. Conversely, we found a strong induction of OC in MC3T3-E1 cells at the mRNA and protein levels only with T3 and not with D3. OC mRNA and protein expression was not detected in NIH fibroblasts. OC GFP transfection experiments indicate rapid transport and secretion of OC, because OC GFP was not found to be accumulated at intracellular compartments after hormone treatment. We conclude that the strong perinuclear immunostaining does not represent OC but a protein immunologically related to OC, as indicated by preabsorption experiments. The expression of this OC epitope-sharing protein is regulated by both D3 and T3 in the osteoblastic MC3T3-E1 and in nonosteogenic cells.

L10 ANSWER 17 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1998162627 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9501010
TITLE: Ceramide-induced apoptosis is mediated by caspase activation independently from retinoblastoma protein post-translational modification.
AUTHOR: Spinedi A; Amendola A; Di Bartolomeo S; Piacentini M
CORPORATE SOURCE: Department of Biology, University of Rome Tor Vergata, Italy.. spinedi@seneca.ccd.utovrm.it
SOURCE: Biochemical and biophysical research communications, (1998 Feb 24) Vol. 243, No. 3, pp. 852-7.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals

ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 10 Apr 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 30 Mar 1998

AB Recent evidence suggests that untimely retinoblastoma protein (RB) dephosphorylation and/or proteolytic degradation might provide key events down-stream cysteine protease (caspase) activation in apoptosis induction. We have dealt with this issue by studying apoptosis induced by N -hexanoylsphingosine (C6-Cer) in CHP-100 human neuroepithelioma cells, maintained in complete growth medium. We report that C6-Cer-induced apoptosis occurred predominantly in G1/S phases of the cycle and was associated with RB dephosphorylation, in the setting of negligible Bcl-2 expression. Apoptosis was also associated with poly(ADP-ribose) polymerase (PARP) cleavage, thus indicating activation of CPP32/Yama/apopain (caspase-3); however, while the tripeptide caspase inhibitor Z-Val-Ala-DL-Asp-fluoromethylketone was able to prevent both C6-Cer-induced PARP cleavage and apoptosis, it was ineffective in preventing RB dephosphorylation. Moreover proteolytic RB cleavage occurred only to a marginal extent after C6-Cer treatment. These results indicate that apoptosis induced by ceramide in CHP-100 cells is caspase-mediated, but RB post-translational modification does not provide a key step, downstream caspase activation, in apoptosis execution.

L10 ANSWER 18 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1998150741 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9491777
TITLE: Anti-Fas induces apoptosis and proliferation in human dermal fibroblasts: differences between foreskin and adult fibroblasts.
AUTHOR: Jelaska A; Korn J H
CORPORATE SOURCE: Department of Medicine, The Arthritis Center, Boston University School of Medicine, Massachusetts 02118, USA.
CONTRACT NUMBER: AR32343 (United States NIAMS NIH HHS)
SOURCE: Journal of cellular physiology, (1998 Apr) Vol. 175, No. 1, pp. 19-29.
Journal code: 0050222. ISSN: 0021-9541.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19 Mar 1998
Last Updated on STN: 19 Mar 1998
Entered Medline: 12 Mar 1998

AB Apoptosis, or programmed cell death, is a naturally occurring process mediated by extracellular signals. We studied anti-Fas (CD95/Apo-1) antibody-induced apoptosis in cultured human foreskin and adult dermal fibroblasts. Induction of apoptosis was identified by fluorescence in situ DNA end-labeling. Anti-Fas antibody induced apoptosis in fibroblasts in a dose- and time-dependent manner. Adult dermal skin fibroblasts were more susceptible to anti-Fas antibody-induced apoptosis than foreskin fibroblasts, with 21-52% dead cells in different strains. In foreskin fibroblasts, anti-Fas antibody (1.0 microg/ml) predominantly induced proliferation ([3H]thymidine incorporation increased to 115-165% of control level) and only low levels of apoptotic cell death after 48 hours of treatment. No induction of proliferation by anti-Fas was found in the adult fibroblasts. Addition of tumor necrosis factor-alpha (TNF-alpha) slightly augmented the anti-Fas antibody-induced apoptosis in

both cell types. When we examined the levels of Fas expression using flow cytometry, we found two- to threefold higher Fas expression in adult fibroblasts. C6-ceramide treatment, which induces Fas-independent apoptosis, gave similar levels of cell death in both foreskin and adult fibroblasts. No proliferation was observed in C6-ceramide-treated fibroblasts. Thus, this difference in apoptosis between adult dermal and foreskin fibroblasts appears to be related to the level of Fas expression. When clones of foreskin fibroblasts were examined, there was heterogeneity of anti-Fas antibody-induced apoptosis and proliferation in the cloned fibroblast subpopulations, but this was not correlated with differences in Fas expression. Alterations in fibroblast populations during the process of differentiation and aging may result from selective loss of apoptosis-susceptible populations.

L10 ANSWER 19 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1998148061 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9478967
TITLE: Enhancement of fibroblast collagenase (matrix metalloproteinase-1) gene expression by ceramide is mediated by extracellular signal-regulated and stress-activated protein kinase pathways.
AUTHOR: Reunanen N; Westermarck J; Hakkinen L; Holmstrom T H; Elo I; Eriksson J E; Kahari V M
CORPORATE SOURCE: Department of Dermatology, Turku University Central Hospital, FIN-20520 Turku, Finland.
SOURCE: The Journal of biological chemistry, (1998 Feb 27) Vol. 273, No. 9, pp. 5137-45.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 7 Apr 1998
Last Updated on STN: 3 Mar 2000
Entered Medline: 25 Mar 1998

AB Inflammatory cytokines tumor necrosis factor-alpha and interleukin-1 trigger the ceramide signaling pathway, initiated by neutral sphingomyelinase-elicited hydrolysis of cell membrane phospholipid sphingomyelin to ceramide, a new lipid second messenger. Here, we show that triggering the ceramide pathway by sphingomyelinase or C2- and C6-ceramide enhances collagenase-1 (matrix metalloproteinase-1; MMP-1) gene expression by fibroblasts. C2-ceramide activates three distinct mitogen-activated protein kinases (MAPKs) in dermal fibroblasts, i.e. extracellular signal-regulated kinase 1/2 (ERK1/2), stress-activated protein kinase/Jun N-terminal-kinase (SAPK/JNK), and p38. Stimulation of MMP-1 promoter activity by C2-ceramide is dependent on the presence of a functional AP-1 cis-element and is entirely inhibited by overexpression of MAPK inhibitor, dual specificity phosphatase CL100 (MAPK phosphatase-1). Activation of MMP-1 promoter by C2-ceramide is also effectively inhibited by kinase-deficient forms of ERK1/2 kinase (MEK1/2) activator Raf-1, ERK1 and ERK2, SAPK/JNK activator SEK1, or SAPKbeta. In addition, ceramide-dependent induction of MMP-1 expression is potently prevented by PD 98059, a selective inhibitor of MEK1 activation, and by specific p38 inhibitor SB 203580. These results show that triggering the ceramide signaling pathway activates MMP-1 gene expression via three distinct MAPK pathways, i.e. ERK1/2, SAPK/JNK, and p38, and suggest that targeted modulation of the ceramide signaling pathway may offer a novel therapeutic approach for inhibiting collagenolytic activity, e.g. in inflammatory disorders.

L10 ANSWER 20 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1998139132 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9499092
TITLE: Distinct pathways for tumor necrosis factor alpha and ceramides in human cytomegalovirus infection.
AUTHOR: Allan-Yorke J; Record M; de Preval C; Davrinche C; Davignon J L
CORPORATE SOURCE: INSERM U.395, Toulouse, France.
SOURCE: Journal of virology, (1998 Mar) Vol. 72, No. 3, pp. 2316-22.
Journal code: 0113724. ISSN: 0022-538X.
Report No.: NLM-PMC109531.
PUB. COUNTRY: United States
DOCUMENT TYPE: (COMPARATIVE STUDY)
Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19 Mar 1998
Last Updated on STN: 19 Mar 1998
Entered Medline: 12 Mar 1998

AB Human cytomegalovirus (HCMV) infection can be fatal to immunocompromised individuals. We have previously reported that gamma interferon and tumor necrosis factor alpha (TNF-alpha) synergistically inhibit HCMV replication in vitro. Ceramides have been described as second messengers induced by TNF-alpha. To investigate the mechanisms involved in the inhibition of HCMV by TNF-alpha, in the present study we have analyzed ceramide production by U373 MG astrocytoma cells and the effects of TNF-alpha versus ceramides on HCMV replication. Our results show that U373 MG cells did not produce ceramides upon incubation with TNF-alpha. Moreover, long-chain ceramides induced by treatment with exogenous bacterial sphingomyelinase inhibited HCMV replication in synergy with TNF-alpha. Surprisingly, short-chain permeant C6-ceramide increased viral replication. Our results show that the anti-HCMV activity of TNF-alpha is independent of ceramides. In addition, our results suggest that TNF-alpha and endogenous long-chain ceramides use separate pathways of cell signalling to inhibit HCMV replication, while permeant C6-ceramide appears to activate a third pathway leading to an opposite effect.

L10 ANSWER 21 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1998119816 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9450998
TITLE: Regulation of Raf-1 kinase by TNF via its second messenger ceramide and cross-talk with mitogenic signalling.
AUTHOR: Muller G; Storz P; Bourteele S; Doppler H; Pfizenmaier K; Mischak H; Philipp A; Kaiser C; Kolch W
CORPORATE SOURCE: Institut fur Zellbiologie und Immunologie, Universitat Stuttgart, Allmandring 31, D-70569 Stuttgart, Germany.
SOURCE: The EMBO journal, (1998 Feb 2) Vol. 17, No. 3, pp. 732-42.
Journal code: 8208664. ISSN: 0261-4189.
Report No.: NLM-PMC1170422.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19 Mar 1998

Last Updated on STN: 3 Mar 2000
Entered Medline: 6 Mar 1998

AB Raf-1 kinase is a central regulator of mitogenic signal pathways, whereas its general role in signal transduction of tumour necrosis factor (TNF) is less well defined. We have investigated mechanisms of Raf-1 regulation by TNF and its messenger ceramide in cell-free assays, insect and mammalian cell lines. In vitro, ceramide specifically bound to the purified catalytic domain and enhanced association with activated Ras proteins, but did not affect the kinase activity of Raf-1. Cell-permeable ceramides induced a marked increase of Ras-Raf-1 complexes in cells co-expressing Raf-1 and activated Ras. Likewise, a fast elevation of the endogeneous ceramide level, induced by TNF treatment of human Kym-1 rhabdomyosarcoma cells, was followed by stimulation of Ras-Raf-1 association without significant Raf-1 kinase activation. Failure of TNF or ceramide to induce Raf-1 kinase was observed in several TNF-responsive cell lines. Both TNF and exogeneous C6-ceramide interfered with the mitogenic activation of Raf-1 and ERK by epidermal growth factor and down-regulated v-Src-induced Raf-1 kinase activity. TNF also induced the translocation of Raf-1 from the cytosolic to the particulate fraction, indicating that this negative regulatory cross-talk occurs at the cell membrane. Interference with mitogenic signals at the level of Raf-1 could be an important initial step in TNF's cytostatic action.

L10 ANSWER 22 OF 44 MEDLINE on STN

ACCESSION NUMBER:	1998081723 MEDLINE
DOCUMENT NUMBER:	PubMed ID: 9421370
TITLE:	Effects of cell-permeable ceramides and tumor necrosis factor-alpha on insulin signaling and glucose uptake in 3T3-L1 adipocytes.
AUTHOR:	Wang C N; O'Brien L; Brindley D N
CORPORATE SOURCE:	Department of Biochemistry, University of Alberta, Edmonton, Canada.
SOURCE:	Diabetes, (1998 Jan) Vol. 47, No. 1, pp. 24-31. Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY:	United States
DOCUMENT TYPE:	Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE:	English
FILE SEGMENT:	Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH:	199801
ENTRY DATE:	Entered STN: 30 Jan 1998 Last Updated on STN: 16 Mar 2003 Entered Medline: 22 Jan 1998

AB Incubation of 3T3-L1 adipocytes with C2- and C6-ceramides (N-acetyl- and N-hexanoylsphingosines) but not dihydro-C2-ceramide increased 2-deoxyglucose uptake in the absence of insulin. This effect was inhibited by PD 98059, LY 294002, and rapamycin, which block the activation of mitogen-activated protein kinase, phosphatidylinositol (PI) 3-kinase, and ribosomal S6 kinase, respectively. Long-term increases in PI 3-kinase activity associated with insulin receptor substrate 1 (IRS-1) increased GLUT1 and GLUT4 concentrations in plasma membranes. This together with increased GLUT1 (but not GLUT4) synthesis explains the increase in non-insulin-dependent glucose uptake. C2-ceramide inhibited insulin-stimulated glucose uptake after 2 h by decreasing insulin-induced translocation of GLUT1 and GLUT4 to plasma membranes. This occurred when there was no increase in basal glucose uptake or decrease in activation of IRS-1 or PI 3-kinase. Incubation for 24 h with tumor necrosis factor-alpha (TNF-alpha) but not C2-ceramide decreased the concentration and insulin-induced tyrosine phosphorylation of IRS-1 in this experimental system. Cell-permeable ceramides mimic some effects of TNF-alpha, especially in stimulating basal

glucose uptake. We identified a site for inhibiting insulin-stimulated glucose uptake that is downstream of PI 3-kinase. Our work provides further mechanisms for the effects of TNF-alpha and ceramides in increasing non-insulin-dependent glucose uptake and decreasing insulin-stimulated uptake in vivo.

L10 ANSWER 23 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1998053902 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9393753
TITLE: The protein kinase C activators phorbol esters and phosphatidylserine inhibit neutral sphingomyelinase activation, ceramide generation, and apoptosis triggered by daunorubicin.
AUTHOR: Mansat V; Laurent G; Levade T; Bettaieb A; Jaffrezou J P
CORPORATE SOURCE: Contrat Jeune Formation, Institut National de la Sante et de la Recherche Medicale 9503, Centre Claudius Regaud, Toulouse, France.
SOURCE: Cancer research, (1997 Dec 1) Vol. 57, No. 23, pp. 5300-4.
Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 12 Mar 1998
Last Updated on STN: 12 Mar 1998
Entered Medline: 2 Mar 1998
AB To address the role of protein kinase C (PKC) in the regulation of ceramide production, we evaluated the impact of the PKC activators 12-O-tetradecanoylphorbol-13-acetate and phosphatidylserine on the apoptotic signaling pathway triggered by the chemotherapeutic drug daunorubicin. Treatment of U937 and HL-60 cells with 0.5-1 microM daunorubicin induced a greater than 30% activation of neutral sphingomyelinase activity within 4-10 min with concomitant sphingomyelin hydrolysis and ceramide generation. Activation of PKC by 12-O-tetradecanoylphorbol-13-acetate and phosphatidylserine inhibited daunorubicin-induced neutral sphingomyelinase activation, sphingomyelin hydrolysis, ceramide generation, and apoptosis. The apoptotic response could be restored by the addition of 25 microM cell-permeant C6-ceramide. In conclusion, PKC emerges as a potentially critical negative regulator of the anthracycline-activated sphingomyelin-ceramide apoptotic pathway.

L10 ANSWER 24 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1997460567 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9314949
TITLE: Evidence that tumor necrosis factor triggers apoptosis in human endothelial cells by interleukin-1-converting enzyme-like protease-dependent and -independent pathways.
AUTHOR: Slowik M R; Min W; Ardito T; Karsan A; Kashgarian M; Pober J S
CORPORATE SOURCE: Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, Connecticut 06536-0812, USA.
CONTRACT NUMBER: HL-36003 (United States NHLBI NIH HHS)
P01-DK38979 (United States NIDDK NIH HHS)
T32-AI0701-21 (United States NIAID NIH HHS)
+
SOURCE: Laboratory investigation; a journal of technical methods and pathology, (1997 Sep) Vol. 77, No. 3, pp.

257-67.
Journal code: 0376617. ISSN: 0023-6837.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199710
ENTRY DATE: Entered STN: 5 Nov 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 23 Oct 1997

AB Cultured human endothelial cells (EC) resist tumor necrosis factor (TNF)-mediated apoptosis. However, the combination of TNF and the protein synthesis inhibitor cycloheximide (CHX) induces apoptosis in up to 50% of EC within 24 hours. TNF + CHX killing is effectively blocked by transfected CrmA protein or treatment with Z-VAD.fmk peptide-both inhibitors of interleukin-1-converting enzyme-like proteases-but not by transfected antiapoptotic proteins Bcl-2, Bcl-XL, or A1. C6-ceramide (cer) can also sensitize EC to TNF-induced apoptosis. TNF + cer killing, which can affect more than 50% of EC, is not effectively inhibited by CrmA or Z-VAD frank, but can be readily blocked by Bcl-2, Bcl-XL, or A1. Both TNF + CHX and TNF+ cer killing are induced by a TNF mutein that only interacts with the type 1 TNF receptor, and both responses can be inhibited by the antiapoptotic protein A20. These data suggest that TNF activates two biochemically separable pathways of EC injury.

L10 ANSWER 25 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1997407929 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9261153
TITLE: Implication of mitochondrial hydrogen peroxide generation in ceramide-induced apoptosis.
AUTHOR: Quillet-Mary A; Jaffrezou J P; Mansat V; Bordier C; Naval J; Laurent G
CORPORATE SOURCE: CJF INSERM 9503, Centre Claudius Regaud, Toulouse Cedex, France.
SOURCE: The Journal of biological chemistry, (1997 Aug 22) Vol. 272, No. 34, pp. 21388-95.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199709
ENTRY DATE: Entered STN: 26 Sep 1997
Last Updated on STN: 10 Dec 2002
Entered Medline: 15 Sep 1997

AB The key events implicated in ceramide-triggered apoptosis remain unknown. In this study we show that 25 microM C6-ceramide induced significant H2O2 production within 60 min, which increased up to 180 min in human myeloid leukemia U937 cells. Inactive analogue dihydro-C6-ceramide had no effect. Furthermore, no H2O2 production was observed in C6-ceramide-treated U937 rho degrees cells, which are mitochondrial respiration-deficient. We also present evidence that ceramide-induced activation of the transcription factors NF-kappaB and AP-1 is mediated by mitochondrial derived reactive oxygen species. Both H2O2 production, transcription factor activation as well as apoptosis could be inhibited by rotenone and thenoyltrifluoroacetone (specific mitochondrial complexes I and II inhibitors) and antioxidants, N-acetylcysteine and pyrrolidine dithiocarbamate. These effects could be potentiated by antimycin A

(specific complex III mitochondrial inhibitor). H2O2 production was also inhibitable by ruthenium red, suggesting a role of mitochondrial calcium homeostasis alterations in ceramide-induced oxidative stress. Finally, C6-ceramide had no influence on mitochondrial membrane potential within the first 6 h. Altogether, our study points to reactive oxygen species, generated at the ubiquinone site of the mitochondrial respiratory chain, as an early major mediator in ceramide-induced apoptosis.

L10 ANSWER 26 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1997382979 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9240970
TITLE: Serine protease inhibitors block neutral sphingomyelinase activation, ceramide generation, and apoptosis triggered by daunorubicin.
AUTHOR: Mansat V; Bettaieb A; Levade T; Laurent G; Jaffrezou J P
CORPORATE SOURCE: CJF INSERM 9503, Centre Claudius Regaud, Toulouse, France.
SOURCE: The FASEB journal : official publication of the Federation of American Societies for Experimental Biology, (1997 Jul) Vol. 11, No. 8, pp. 695-702.
Journal code: 8804484. ISSN: 0892-6638.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199708
ENTRY DATE: Entered STN: 2 Sep 1997
Last Updated on STN: 2 Sep 1997
Entered Medline: 19 Aug 1997
AB To address the role of a plausible protease cascade in daunorubicin-triggered apoptosis, we evaluated the effect of cell-permeant protease inhibitors on its signal transduction pathway. Treatment of U937 and HL-60 cells with 0.5-1 microM of the chemotherapeutic drug daunorubicin induced a greater than 30% activation of neutral sphingomyelinase activity within 4-10 min with concomitant sphingomyelin hydrolysis and ceramide generation. DNA fragmentation and the classical morphological features of apoptosis were observed within 4-6 h. Pretreatment of cells with the serine protease inhibitors N-tosyl-L-phenylalanyl chloromethyl ketone (20 microM) or dichloroisocoumarin (20 microM) for 30 min inhibited daunorubicin-induced neutral sphingomyelinase activation, sphingomyelin hydrolysis, ceramide generation, and apoptosis. Other cell-permeant protease inhibitors such as pepstatin, leupeptin, and antipain had no such effect. The apoptotic response could be restored by the addition of 25 microM cell-permeant C6-ceramide. Daunorubicin-induced NF-kappaB activation was inhibited by dichloroisocoumarin but not by N-tosyl-L-phenylalanyl chloromethyl ketone, suggesting that this transcription factor can be activated independently of ceramide and is not directly implicated in the apoptotic pathway. These results suggest that inhibitors of serine proteases can act upstream of ceramide in drug-triggered apoptosis and that neutral sphingomyelinase activation is either directly or indirectly serine protease dependent.

L10 ANSWER 27 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1997347536 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9202042
TITLE: Phospholipase A2 is necessary for tumor necrosis factor alpha-induced ceramide generation in L929 cells.
AUTHOR: Jayadev S; Hayter H L; Andrieu N; Gamard C J; Liu B; Balu R; Hayakawa M; Ito F; Hannun Y A
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center,

Durham, North Carolina 27710, USA.
CONTRACT NUMBER: GM-43825 (United States NIGMS NIH HHS)
SOURCE: The Journal of biological chemistry, (1997 Jul 4) Vol. 272, No. 27, pp. 17196-203. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 12 Aug 1997
Last Updated on STN: 12 Aug 1997
Entered Medline: 31 Jul 1997

AB The role of cytosolic phospholipase A2 (cPLA2) in the regulation of ceramide formation was examined in a cell line (L929) responsive to the cytotoxic action of tumor necrosis factor alpha (TNFalpha). In L929 cells, the addition of TNFalpha resulted in the release of arachidonate, which was followed by a prolonged accumulation of ceramide occurring over 5-12 h and reaching 250% over base line. The formation of ceramide was accompanied by the hydrolysis of sphingomyelin and the activation of three distinct sphingomyelinases (neutral Mg2+-dependent, neutral Mg2+-independent, and acidic enzymes). The variant cell line C12, which lacks cPLA2, is resistant to the cytotoxic action of TNFalpha. TNFalpha was able to activate nuclear factor kappaB in both the wild-type L929 cells and the C12 cells. However, TNFalpha was unable to cause the release of arachidonate or the accumulation of ceramide in C12 cells. C6-ceramide overcame the resistance to TNFalpha and caused cell death in C12 cells to a level similar to that in L929 cells. The introduction of the cPLA2 gene into C12 cells resulted in partial restoration of TNFalpha-induced arachidonate release, ceramide accumulation, and cytotoxicity. This study suggests that cPLA2 is a necessary component in the pathways leading to ceramide accumulation and cell death.

L10 ANSWER 28 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1997327724 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9210401
TITLE: Inhibition of the expression of ornithine decarboxylase and c-Myc by cell-permeant ceramide in difluoromethylornithine-resistant leukaemia cells.
AUTHOR: Flamigni F; Faenza I; Marmiroli S; Stanic' I; Giaccari A; Muscari C; Stefanelli C; Rossoni C
CORPORATE SOURCE: Dipartimento di Biochimica 'G.Moruzzi', Universita di Bologna, via Irnerio 48, 40126 Bologna, Italy.
SOURCE: The Biochemical journal, (1997 Jun 15) Vol. 324 (Pt 3), pp. 783-9. Journal code: 2984726R. ISSN: 0264-6021. Report No.: NLM-PMC1218493.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199707
ENTRY DATE: Entered STN: 12 Aug 1997
Last Updated on STN: 12 Aug 1997
Entered Medline: 28 Jul 1997

AB Ceramide has emerged as a novel lipid mediator in cell growth and apoptosis. In difluoromethylornithine-resistant L1210 cells stimulated to growth from quiescence, the cell-permeant analogues of ceramide N-acetylsphingosine (C2-ceramide) and N-

hexanoylsphingosine (C6-ceramide) inhibited the induction of ornithine decarboxylase (ODC) activity with IC50 of 8.3 and 1.5 microM respectively. This effect was strictly related to the ability to inhibit cell growth and [3H]thymidine incorporation. The suppression of cell growth was also associated with apoptosis. The addition of bacterial sphingomyelinase resulted in a significant, but limited, reduction of ODC induction and [3H]thymidine incorporation. Bacterial lipopolysaccharide, which may act as a ceramide analogue, also inhibited the induction of the enzyme. Moreover, C6-ceramide largely prevented the accumulation of ODC mRNA and its precursor, ODC heterogeneous nuclear RNA, that accompanied the induction of ODC activity. A slight increase in ODC turnover was also observed. The DNA-binding activity of some transcription factors known to bind and transactivate the ODC gene was investigated by gel mobility-shift assay under the same experimental conditions. However, only the binding of Myc/Max was negatively affected by the treatment with C6-ceramide. Furthermore, the amount of immunoreactive c-Myc, which increased after stimulation of the cells to growth, was strongly reduced by C6-ceramide. These results suggest that the inhibition of c-Myc and ODC expression may be early events in the response of leukaemia cells to ceramide.

L10 ANSWER 29 OF 44 MEDLINE on STN

ACCESSION NUMBER: 1997319195 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9176098
TITLE: C2-ceramide and C6-ceramide inhibited priming for enhanced release of superoxide in monocytes, but had no effect on the killing of leukaemic cells by monocytes.
AUTHOR: Nakabo Y; Pabst M J
CORPORATE SOURCE: Department of Oral Biology, University of Tennessee, Memphis 38163, USA.
CONTRACT NUMBER: DE05474 (United States NIDCR NIH HHS)
DE11125 (United States NIDCR NIH HHS)
SOURCE: Immunology, (1997 Apr) Vol. 90, No. 4, pp. 477-82.
Journal code: 0374672. ISSN: 0019-2805.
Report No.: NLM-PMC1456677.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199706
ENTRY DATE: Entered STN: 9 Jul 1997
Last Updated on STN: 3 Mar 2000
Entered Medline: 23 Jun 1997

AB Ceramide acts as an intracellular second messenger in cellular signal transduction. We examined the effects of two cell-permeable ceramides, C2-ceramide and C6-ceramide, on human monocyte functions. After monocytes were primed with lipopolysaccharide (LPS) or interferon-gamma (IFN-gamma) for 18 hr in suspension culture, they produced a high amount of superoxide (O2-) when triggered by phorbol myristate acetate. C2- or C6-ceramide inhibited O2- release from monocytes primed with LPS (1 ng/ml) or IFN-gamma (100 U/ml), but did not affect unprimed monocytes. An analogue, C2-dihydroceramide, was inactive. C2-ceramide was most effective at 6 microM, and C6-ceramide at 60 microM. C2- or C6-ceramide at these concentrations was not toxic for monocytes, as assessed by trypan blue exclusion and by the 3-[4, 5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay which measures the ability of live cells to produce formazan. C2-ceramide (20 microM) had no effect on the killing

of leukaemic cells (HL-60 and K562 cells) by monocytes treated with IFN-gamma, LPS, or both for 18 hr, with killing assessed by an 111 Indium-releasing assay. C2-ceramide (20 microM) induced secretion of low amounts of tumour necrosis factor-alpha (TNF-alpha) and interleukin-1 beta (IL-1 beta) from the monocytes. But C2-ceramide did not alter the higher secretion of TNF-alpha or IL-1 beta from monocytes treated with IFN-gamma or LPS. Thus the cell-permeable ceramides acted like antagonists of LPS, rather than analogues of LPS, as has been proposed. The results here showed that the signal transduction pathway for O2- release by monocytes differed from that for the cytolysis of leukaemic cells, and confirmed that oxygen radicals are not involved in cytolysis.

L10 ANSWER 30 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1997269045 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9111045
TITLE: Direct effect of ceramide on the mitochondrial electron transport chain leads to generation of reactive oxygen species. Role of mitochondrial glutathione.
AUTHOR: Garcia-Ruiz C; Colell A; Mari M; Morales A; Fernandez-Checa J C
CORPORATE SOURCE: Instituto Investigaciones Biomedicas, Consejo Superior Investigaciones Cientificas, Universidad de Barcelona, Barcelona 08036, Spain.
CONTRACT NUMBER: AA09526 (United States NIAAA NIH HHS)
SOURCE: The Journal of biological chemistry, (1997 Apr 25) Vol. 272, No. 17, pp. 11369-77.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199705
ENTRY DATE: Entered STN: 2 Jun 1997
Last Updated on STN: 2 Jun 1997
Entered Medline: 21 May 1997

AB Ceramide is a sphingolipid that is generated in the signaling of inflammatory cytokines such as tumor necrosis factor (TNF), which exerts many functional roles depending on the cell type where it is produced. Since TNF cytotoxicity is mediated by overproduction of reactive oxygen species from mitochondria, we have examined the role of ceramide in generation of oxidative stress in isolated rat liver mitochondria. The present studies demonstrate that addition of N-acetylsphingosine (C2-ceramide) to mitochondria led to an increase of fluorescence of dihydrorhodamine 123 or dichlorofluorescein-stained mitochondria, indicating formation of hydrogen peroxide. Such effect was significant at 0.25 microM and maximal at 1-5 microM C2, decreasing at greater concentrations. This inductive effect of ceramide was mimicked by N-hexanoylsphingosine at the same concentration range, whereas the immediate precursor of C2, C2-dihydroceramide increased hydrogen peroxide at 1-5 microM. Sphingosine generated hydrogen peroxide at concentrations >/=10 microM, whereas diacylglycerol failed to increase hydrogen peroxide. The increase in hydrogen peroxide induced by C2 was not triggered by mitochondrial permeability transition as C2 did not induce mitochondrial swelling. Blocking electron transport chain at complex I and II prevented the increase in hydrogen peroxide induced by C2; however, interruption of electron flow at complex III by antimycin A potentiated the inductive effect of C2. Depletion of matrix GSH prior to exposure to ceramide resulted in a potentiated increase (2-fold) of hydrogen peroxide generation, leading to lipid peroxidation and loss of

activity of respiratory chain complex IV compared with GSH-repleted mitochondria. Mitochondria isolated from TNF-treated cells showed an increase (2-3-fold) in the amount of ceramide compared with mitochondria from untreated cells. These results suggest that mitochondria are a target of ceramide produced in the signaling of TNF whose effect on mitochondrial electron transport chain leads to overproduction of hydrogen peroxide and consequently this phenomena may account for the generation of reactive oxygen species during TNF cytotoxicity.

L10 ANSWER 31 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1997207244 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9054379
TITLE: Alteration of the sphingomyelin/ceramide pathway is associated with resistance of human breast carcinoma MCF7 cells to tumor necrosis factor-alpha-mediated cytotoxicity.
AUTHOR: Cai Z; Bettaieb A; Mahdani N E; Legres L G; Stancou R; Masliah J; Chouaib S
CORPORATE SOURCE: INSERM Contrat Jeune Formation 94-11 "Cytokines et Immunite Antitumorale," Institut Gustave Roussy, 94805 Villejuif, France.
SOURCE: The Journal of biological chemistry, (1997 Mar 14) Vol. 272, No. 11, pp. 6918-26. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199704
ENTRY DATE: Entered STN: 24 Apr 1997 Last Updated on STN: 24 Apr 1997 Entered Medline: 17 Apr 1997

AB The interference of tumor necrosis factor-alpha (TNF) signaling processes with the acquisition of tumor resistance to TNF was investigated using the TNF-sensitive human breast carcinoma MCF7 cell line and its established TNF-resistant variant (R-A1). The resistance of R-A1 cells to TNF correlated with a low level of p55 TNF receptor expression and an absence of TNF signaling through TNF receptors. Stable transfection of wild-type p55 receptor in R-A1 resulted in enhancement of p55 expression and in partial restoration of TNF signaling, including nuclear factor-kappaB (NF-kappaB) activation. However, the transfected cells remained resistant to TNF-induced apoptosis. Northern blot analysis revealed a comparable induction of manganous superoxide dismutase and A20 mRNA expression in p55-transfected cells and in sensitive MCF7 cells, making it unlikely that these genes are involved in the resistance to TNF-mediated cytotoxicity. While TNF significantly stimulated both neutral and acidic sphingomyelinase (SMase) activities with concomitant sphingomyelin (SM) hydrolysis and ceramide generation in MCF7, it failed to trigger these events in TNF-resistant p55-transfected cells. In addition, the basal SM content was significantly higher in sensitive MCF7 as compared to the resistant counterparts. Furthermore, the TNF-resistant cells tested could be induced to undergo cell death after exposure to exogenous SMase or cell-permeable C6-ceramide. This study also shows that TNF failed to induce arachidonic acid release in p55-transfected resistant cells, suggesting that an alteration of phospholipase A2 activation may be associated with MCF7 cell resistance to TNF. Our findings strongly suggest a role of ceramide in the mechanism of cell resistance to TNF-mediated cell death and may be relevant in elucidating the biochemical nature of intracellular messengers leading to such resistance.

L10 ANSWER 32 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1997054590 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8898887
TITLE: Induction of programmed cell death and immunosuppression by exogenous sphingolipids are separate processes.
AUTHOR: Olshefski R; Taylor B; Heitger A; Hasegawa A; Ladisch S
CORPORATE SOURCE: Center for Cancer and Transplantation Biology, Children's National Medical Center, George Washington University School of Medicine, Washington, DC 20010-2970, USA.
CONTRACT NUMBER: CA42361 (United States NCI NIH HHS)
CA61010 (United States NCI NIH HHS)
SOURCE: European journal of biochemistry / FEBS, (1996 Oct 1) Vol. 241, No. 1, pp. 47-55.
Journal code: 0107600. ISSN: 0014-2956.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 5 Dec 1996
AB Gangliosides are highly immunosuppressive molecules but the mechanism(s) by which they act upon cells remains to be fully defined. Several metabolic products of exogenous gangliosides, including ceramide, have recently been suggested as second messengers in programmed cell death (PCD). Therefore, we have probed the role of gangliosides and ceramides in the induction of PCD and in the inhibition of in vitro lymphoproliferation. PCD was caused only by exogenous ceramides with short fatty acyl groups-d18:1-C2:0 (C2-ceramide, where d18:1 is sphingosine and C2:O is an acetyl group) and d18:1-C6:0 (C6-ceramide, where C6:O is a hexanoyl group). None of the gangliosides studied induced PCD, including naturally occurring GM3, synthetic d18:1-C18:0 GM3 (C18-Cer GM3, where C18:0 is a stearoyl group), or even d18:1-C2:0 GM3 (C2-Cer GM3), which itself contains a PCD-causing ceramide. However, these gangliosides were highly immunosuppressive, inhibiting antigen-induced lymphoproliferation at micromolar concentrations. We conclude that exogenous sphingolipids cause inhibition of lymphoproliferation and PCD by two separate and distinct mechanisms of action.

L10 ANSWER 33 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1997024438 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8870666
TITLE: Lipid mediators of insulin resistance: ceramide signalling down-regulates GLUT4 gene transcription in 3T3-L1 adipocytes.
AUTHOR: Long S D; Pekala P H
CORPORATE SOURCE: Department of Biochemistry, School of Medicine, East Carolina University, Greenville, NC 27858, USA.
CONTRACT NUMBER: GM32892 (United States NIGMS NIH HHS)
SOURCE: The Biochemical journal, (1996 Oct 1) Vol. 319 (Pt 1), pp. 179-84.
Journal code: 2984726R. ISSN: 0264-6021.
Report No.: NLM-PMC1217752.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English

FILE SEGMENT: Priority Journals
ENTRY MONTH: 199612
ENTRY DATE: Entered STN: 28 Jan 1997
Last Updated on STN: 28 Jan 1997
Entered Medline: 3 Dec 1996

AB We have previously demonstrated that chronic exposure of 3T3-L1 adipocytes to tumour necrosis factor-alpha (TNF) resulted in a marked decrease (approximately 90%) in cellular GLUT4 (insulin-responsive glucose transporter) mRNA content as a result of a decreased transcription rate of the GLUT4 gene (approximately 75%) and a reduced half-life of its mRNA (9 to 4.5 h). Investigation of the signalling mechanism responsible for this regulation demonstrated that in the 3T3-L1 adipocytes, sphingomyelin levels decreased to 50% of control levels within 40 min of exposure to TNF, consistent with activation of a sphingomyelinase. In the same manner as with TNF, treatment of the adipocytes with 1-3 microM C6-ceramide, a membrane-permeable analogue of ceramide, decreased GLUT4 mRNA content by approximately 60%. Subsequent investigations revealed that transcription of the GLUT4 gene was reduced by approximately 65% in response to C6-ceramide, demonstrating that the decrease in mRNA content is mediated by a reduction in the transcription of the genc. No effect on GLUT4 mRNA stability was observed after exposure of the adipocytes to C6-ceramide. These observations are interesting in light of our previous data demonstrating that TNF affects both GLUT4 transcription and mRNA stability in the 3T3-L1 adipocytes. In conclusion, the effect of ceramide on GLUT4 gene expression is at the level of transcription, suggesting that another pathway controls mRNA stability. These data establish that ceramide-initiated signal transduction pathways exist within the adipocyte, and provide a potential mechanism for control of GLUT4 gene expression.

L10 ANSWER 34 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1996355508 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8702918
TITLE: c-Jun is a downstream target for ceramide-activated protein phosphatase in A431 cells.
AUTHOR: Reyes J G; Robayna I G; Delgado P S; Gonzalez I H; Aguiar J Q; Rosas F E; Fanjul L F; Galarreta C M
CORPORATE SOURCE: Departamento de Endocrinologia Celular y Molecular, Universidad de Las Palmas, School of Medicine, Las Palmas 35016, Spain.
SOURCE: The Journal of biological chemistry, (1996 Aug 30) Vol. 271, No. 35, pp. 21375-80.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199610
ENTRY DATE: Entered STN: 22 Oct 1996
Last Updated on STN: 3 Mar 2000
Entered Medline: 10 Oct 1996

AB Stimulation of [3H]serine-labeled A431 cells with tumor necrosis factor-alpha (TNFalpha) or bacterial sphingomyelinase (SMase) resulted in a rapid decrease (approximately 50% by 15 min) in cellular [3H]sphingomyelin content and generation of the lipid moiety [3H]ceramide, which remained elevated 60 min later. Sphingomyelin hydrolysis in response to TNFalpha or bacterial SMase resulted in a time-dependent decrease in the phosphorylation state of c-Jun protein, an effect that was also observed in cells treated with the membrane-permeable ceramide analogue N-hexanoylsphingosine (C6-

ceramide). The rapid dephosphorylation of the c-Jun gene product in response to TNFalpha, SMase, or C6-ceramide was not observed in A431 cells treated with the serine-threonine phosphatase inhibitor okadaic acid. After the initial steps of previously described methods for the purification of a ceramide-activated protein phosphatase termed CAPP (Dobrowsky, R. T., Kamibayashi, C., Mumby, M. C., and Hannun, Y. A. (1993) J. Biol. Chemical 268, 15523-15530), we obtained a cytosolic fraction from A431 cells that specifically dephosphorylated 32Pi-labeled c-Jun protein used as substrate in an immunocomplex phosphatase assay. Phosphatase activity in vitro was apparent only in the presence of ceramide (5 micro) and was specifically abrogated when okadaic acid (1 n) was included in the immunocomplex phosphatase assay. These results provide strong evidence for c-Jun as a downstream target for CAPP activated in response to post-TNF signaling in A431 cells.

L10 ANSWER 35 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1996278722 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8662781
TITLE: Ceramide inactivates cellular protein kinase Calpha.
AUTHOR: Lee J Y; Hannun Y A; Obeid L M
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710, USA.
CONTRACT NUMBER: 5T32 AG00029 (United States NIA NIH HHS)
K08AG00520 (United States NIA NIH HHS)
SOURCE: The Journal of biological chemistry, (1996 May 31) Vol. 271, No. 22, pp. 13169-74.
Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199608
ENTRY DATE: Entered STN: 22 Aug 1996
Last Updated on STN: 22 Aug 1996
Entered Medline: 15 Aug 1996

AB Ceramide mediates the effects of extracellular agents on cellular growth, differentiation and apoptosis. In this study, we explored the mechanisms by which ceramide induces its cellular effects. In Molt-4 cells, phorbol 12-myristate 13-acetate (PMA) induced retinoblastoma gene product (Rb) phosphorylation, and ceramide inhibited this effect, suggesting an inhibitory effect of ceramide on the protein kinase C (PKC) pathway, the primary target of PMA. Molt-4 cells contained primarily PKCalpha and betaII isoforms of PKC. To determine the effects of ceramide on PKC, we developed an immunoprecipitation assay for PKCalpha activity. Exposure of Molt-4 cells to C6-ceramide resulted in a concentration and time-dependent inhibition of immunoprecipitated protein kinase Calpha (PKCalpha). Initial inhibition was observed as early as 4.5 h after treatment of cells with C6-ceramide, and the activity was completely lost by 13 h. Inhibition of PKCalpha activity was seen at concentrations of ceramide as low as 5 microM with maximal effects occurring at a concentration of 15 microM. Both C2 and C6-ceramide were inhibitory, but C2 and C6 dihydroceramides were not. Ceramide did not directly inhibit PKCalpha in vitro or modulate the levels of PKCalpha protein, suggesting that ceramide acted indirectly. Moreover, ceramide did not inhibit PMA-induced translocation of PKCalpha. Taken together, these results suggested that ceramide caused inactivation of PKCalpha. Since PKC requires phosphorylation for activity, we determined the effects of ceramide on phosphorylation of PKCalpha. C6-ceramide inhibited basal and PMA-induced phosphorylation of PKCalpha. In addition, okadaic acid, a potent phosphatase inhibitor, slightly stimulated PKC activity and blocked the effects of ceramide on

PKCalpha inhibition. These results demonstrate that ceramide causes inhibition/inactivation of PKCalpha and suggest these effects of ceramide may be mediated by a protein phosphatase.

L10 ANSWER 36 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1996219977 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8639901
TITLE: Phosphatase 2A participates in interferon-gamma's induced upregulation of C1 inhibitor mRNA expression.
AUTHOR: Heda G D; Kehoe K J; Mahdi F; Schmaier A H
CORPORATE SOURCE: Thrombosis Research Center, Temple University School of Medicine, Philadelphia, PA, USA.
CONTRACT NUMBER: HL01615 (United States NHLBI NIH HHS)
HL45486 (United States NHLBI NIH HHS)
SOURCE: Blood, (1996 Apr 1) Vol. 87, No. 7, pp. 2831-8.
Journal code: 7603509. ISSN: 0006-4971.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 26 Jul 1996
Last Updated on STN: 3 Feb 1997
Entered Medline: 18 Jul 1996

AB C1 inhibitor (C1 INH) is the major inhibitor of the proteolytically active subcomponents of C1, kallikrein, activated forms of factor XII, and factor XIa in plasma. We determined the mechanism(s) how interferon-gamma (IFN-gamma) regulates C1 INH mRNA expression in HepG2 cells. Cycloheximide or anisomycin treatment alone did not increase C1 INH mRNA nor did it potentiate C1 INH mRNA expression after IFN-gamma stimulation. C1 INH mRNA levels on Northern blot from untreated and IFN-gamma-treated cells did not change for more than 20 hours after actinomycin D treatment. Actinomycin D and 5,6-dichloro-1-beta-ribofuranosylbenzimidazole abolished IFN-gamma-induced C1 INH mRNA expression. Relatively more C1 INH mRNA precursor (heterogeneous nuclear RNA [hnRNA]) was detected in total RNA from IFN-gamma-treated HepG2 cells than unstimulated cells. Treatment of HepG2 cells with the phosphatase 1 and 2A inhibitors, okadaic acid (> or = 50 nmol/L) and calyculin (> or = 25 nmol/L), decreased IFN-gamma's ability to upregulated C1 INH mRNA. The phosphatase 2A inhibitor, cantharidin (> or = 10 micromol/L), also blocked the IFN-gamma induction of the C1 INH gene. In HepG2 cells total phosphatase 2A activity was significantly increased by C6 ceramide but not IFN-gamma. However, C6 ceramide itself did not increase C1 INH mRNA expression. These data indicate that phosphatase 2A is required to dephosphorylate a substrate in order for IFN-gamma to induce the transcriptional upregulation of C1 INH mRNA, but phosphatase 2A is not a direct stimulator of C1 INH gene expression.

L10 ANSWER 37 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1996185006 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8612681
TITLE: Morphological differentiation of N1E-115 neuroblastoma cells by dimethyl sulfoxide activation of lipid second messengers.
AUTHOR: Clejan S; Dotson R S; Wolf E W; Corb M P; Ide C F
CORPORATE SOURCE: Department of Pathology, Tulane University School of Medicine, New Orleans, Louisiana 70112, USA.
SOURCE: Experimental cell research, (1996 Apr 10) Vol. 224, No. 1, pp. 16-27.
Journal code: 0373226. ISSN: 0014-4827.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, U.S. GOV'T, NON-P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199606
ENTRY DATE: Entered STN: 13 Jun 1996
Last Updated on STN: 6 Feb 1998
Entered Medline: 5 Jun 1996

AB Quantitative changes in the lipid second messenger diacylglycerol (DAG) were studied in the rat neuroblastoma N1E-115 following exposure to the differentiating agent dimethylsulfoxide (DMSO). Relatively high basal levels of DAG are present in these cells, and addition of 2% DMSO elicited a biphasic increase in DAG levels, dependent on the presence of extracellular Ca2+. Exposure to DMSO also elicited a rapid increase in inositol phosphate and a slight increase in phosphatidic acid (PA), trailing that of DAG. The molecular species (MS) of DAG were analyzed. Within 60 s of DMSO application there were transient increases of DAG representative of phosphatidylinositol (PI) hydrolysis. At longer intervals, more DAG originated from phosphatidylcholine. The MS composition of newly formed PA resembled that of PI and native DAG. Inhibition studies indicated that DAG is formed in the DMSO-treated cells by phospholipases C and that PA formed later is a result of DAG phosphorylation and not activity of phospholipase D (PLD). Undifferentiated cells exhibited an active PLD pathway. In contrast, PLD in DMSO-differentiated cells was not active. In examining the involvement of the sphingomyelin pathway, DMSO exposure was found to increase ceramide levels with a concomitant decrease in sphingomyelin. Addition of the exogenous, soluble analog C6-ceramide to undifferentiated cells resulted in dramatic reductions in DAG and PA levels and PLD activity. These results indicate that DMSO treatment inactivates PLD while activating phospholipases C and the sphingomyelin pathway, suggesting a "switch" between signal transduction pathways in the undifferentiated and differentiated states of N1E-115.

L10 ANSWER 38 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1995183463 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7877980
TITLE: Retinoblastoma gene product as a downstream target for a ceramide-dependent pathway of growth arrest.
AUTHOR: Dbaibo G S; Pushkareva M Y; Jayadev S; Schwarz J K; Horowitz J M; Obeid L M; Hannun Y A
CORPORATE SOURCE: Department of Pediatrics, Duke University Medical Center, Durham, NC 27710.
CONTRACT NUMBER: GM43825 (United States NIGMS NIH HHS)
SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1995 Feb 28) Vol. 92, No. 5, pp. 1347-51.
Journal code: 7505876. ISSN: 0027-8424.
Report No.: NLM-PMC42516.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
(RESEARCH SUPPORT, NON-U.S. GOV'T)
(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 199504
ENTRY DATE: Entered STN: 19 Apr 1995
Last Updated on STN: 29 Oct 2002
Entered Medline: 4 Apr 1995

AB Ceramide, a lipid mediator, has been most closely associated with antiproliferative activities. In this study, we examine the mechanism by

which ceramide induces growth suppression and the role of the retinoblastoma gene product (Rb) in this process. Withdrawal of serum from the serum-dependent MOLT-4 cells resulted in significant dephosphorylation of Rb, correlating with the induction of G0/G1 cell cycle arrest. Serum withdrawal resulted in marked elevation in the levels of endogenous ceramide (3-fold at 24 h and 8-fold at 96 h) with little changes in the endogenous levels of sphingosine. The addition of exogenous C6-ceramide resulted in a concentration- and time-dependent dephosphorylation of Rb. Exogenous ceramide was active at levels comparable to endogenous levels achieved with serum withdrawal. Peak activity of exogenous ceramide (at 6 h) correlated with the uptake of C6-ceramide by MOLT-4 cells. Next, a number of studies were conducted to determine whether Rb plays a role in ceramide-induced growth suppression. (i) C6-Ceramide was poorly active in growth suppression of retinoblastoma cells that lack Rb. (ii) Mink lung epithelial cells in which Rb had been sequestered by overexpression of large tumor antigen were resistant to the action of ceramide compared to cells transfected with large tumor antigen mutated in the Rb-binding pocket. (iii) Overexpression of the E1A adenoviral protein, which binds and sequesters Rb, resulted in protection from growth suppression and cell cycle arrest induced by ceramide. Thus, these studies demonstrate that Rb is a downstream target for ceramide and may function in a growth suppressor pathway resulting in cell cycle arrest.

L10 ANSWER 39 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1995070325 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7979551
TITLE: Keratinocyte differentiation is induced by cell-permeant ceramides and its proliferation is promoted by sphingosine.
AUTHOR: Wakita H; Tokura Y; Yagi H; Nishimura K; Furukawa F; Takigawa M
CORPORATE SOURCE: Department of Dermatology, Hamamatsu University School of Medicine, Japan.
SOURCE: Archives of dermatological research, (1994) Vol. 286, No. 6, pp. 350-4.
Journal code: 8000462. ISSN: 0340-3696.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199412
ENTRY DATE: Entered STN: 10 Jan 1995
Last Updated on STN: 3 Feb 1997
Entered Medline: 19 Dec 1994

AB Ceramide and sphingosine have been suggested to be intracellular modulators of cell growth and differentiation. The effects of these sphingolipids on the growth and differentiation of keratinocytes were examined using cultured human keratinocytes (the squamous cell carcinoma cell line, DJM-1). The synthetic short-chain cell-permeant analogues of ceramides, N-acetylsphingosine, N-hexanoylsphingosine and N-octanoylsphingosine, significantly promoted differentiation as confirmed by upregulation of cornified envelope formation, synthesis of involucrin and increased transglutaminase activity, and inhibited proliferation as shown by a reduction in cell numbers, DNA amount and thymidine incorporation. Generally, these activities were greater the longer the N-acyl carbon chain. On the other hand, sphingosine at an appropriate concentration modestly stimulated the proliferation of cultured cells. Our results suggest the possibility that the growth and differentiation of keratinocytes are at least partially regulated by ceramide and sphingosine.

L10 ANSWER 40 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1994012813 MEDLINE
DOCUMENT NUMBER: PubMed ID: 8408075
TITLE: Detection and characterization of ceramide-1-phosphate phosphatase activity in rat liver plasma membrane.
AUTHOR: Boudker O; Futerman A H
CORPORATE SOURCE: Department of Membrane Research and Biophysics, Weizmann Institute of Science Rehovot, Israel.
SOURCE: The Journal of biological chemistry, (1993 Oct 15) Vol. 268, No. 29, pp. 22150-5. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199311
ENTRY DATE: Entered STN: 17 Jan 1994
Last Updated on STN: 3 Feb 1997
Entered Medline: 18 Nov 1993

AB A calcium-dependent ceramide (Cer) kinase was recently detected in human leukemia (HL-60) cells (Kolesnick, R.N., and Hemer, M.R. (1990) J. Biol. Chemical 265, 18803-18808) where it may function in terminating the regulatory effects of Cer, and in synaptic vesicles (Bajjalieh, S. M., Martin, T. F. J., and Floor, E. (1989) J. Biol. Chemical 264, 14354-14360). We now demonstrate that the addition of both Cer-1-phosphate (Cer-1-P) and a short-acyl chain analog of Cer-1-P, N-hexanoylsphingosine-1-phosphate (C6-Cer-1-P) to cultured cells and a variety of subcellular fractions results in rapid degradation to Cer and C6-Cer, respectively. The Cer-1-P phosphatase activity is enriched in a rat liver plasma membrane fraction and appears to be distinct from the phosphatase that hydrolyzes phosphatidic acid (PA), PA phosphohydrolase, as shown by the difference in sensitivity of Cer-1-P and PA hydrolysis to propranolol, detergent, and heat treatment. Moreover, the Km of Cer-1-P hydrolysis is 10-fold lower than the Km of PA hydrolysis in plasma membrane. PA is a noncompetitive inhibitor of Cer-1-P hydrolysis, with an inhibition constant 1-1.5-fold higher than the Km of Cer-1-P hydrolysis. In contrast, Cer-1-P does not inhibit PA hydrolysis. Finally, we describe the synthesis of a novel analog of Cer-1-P which is not hydrolyzed in vitro and in vivo and is internalized in cultured cells by endocytosis. These results are discussed in relation to the possible roles of Cer-1-P in regulating intracellular levels of Cer.

L10 ANSWER 41 OF 44 MEDLINE on STN
ACCESSION NUMBER: 1993315414 MEDLINE
DOCUMENT NUMBER: PubMed ID: 7686898
TITLE: Sphingomyelinase and ceramide activate mitogen-activated protein kinase in myeloid HL-60 cells.
AUTHOR: Raines M A; Kolesnick R N; Golde D W
CORPORATE SOURCE: Molecular Pharmacology and Therapeutics Program, Memorial Sloan-Kettering Cancer Center, New York, New York 10021.
CONTRACT NUMBER: P30 CA08748 (United States NCI NIH HHS)
R01 HL42107 (United States NHLBI NIH HHS)
R37 CA30388 (United States NCI NIH HHS)
+
SOURCE: The Journal of biological chemistry, (1993 Jul 15) Vol. 268, No. 20, pp. 14572-5. Journal code: 2985121R. ISSN: 0021-9258.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (RESEARCH SUPPORT, NON-U.S. GOV'T)

(RESEARCH SUPPORT, U.S. GOV'T, P.H.S.)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199308
ENTRY DATE: Entered STN: 20 Aug 1993
Last Updated on STN: 3 Mar 2000
Entered Medline: 12 Aug 1993

AB Mechanisms involved in tumor necrosis factor (TNF)-alpha signal transduction are incompletely understood. In some circumstances, TNF may use a signal transduction pathway involving hydrolysis of sphingomyelin to ceramide and stimulation of a ceramide-activated protein kinase. In HL-60 cells, TNF rapidly activates this pathway and induces monocytic differentiation. Here, we demonstrate that treatment of HL-60 cells with TNF selectively increases tyrosine phosphorylation of p42 mitogen-activated protein kinase (p42mapk) and stimulates its enzymatic activity. Induction of p42mapk phosphorylation was time- and dose-dependent and closely paralleled activation of sphingomyelin hydrolysis. Direct engagement of the sphingomyelin signal transduction pathway by addition of bacterial sphingomyelinase led to MAP kinase activation. The time course of p42mapk phosphorylation in the sphingomyelinase-treated cells was similar to that of TNF, with maximal response occurring at 5 min. A maximal concentration of sphingomyelinase (0.01 unit/ml) was more potent than TNF at inducing MAP kinase enzymatic activity (2.6-fold) and phosphorylation of MAP kinase and tyrosine. The cell-permeable ceramide analogs, C2- and C6-ceramide, which mimic effects of TNF, also induced p42mapk phosphorylation within seconds. These studies indicate that the sphingomyelin pathway can regulate MAP kinase activity and suggest that MAP kinase activation by this mechanism may be involved in TNF-induced signal transduction.

L10 ANSWER 42 OF 44 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 2000:1544 BIOSIS
DOCUMENT NUMBER: PREV200000001544
TITLE: Bcl-2 and mitochondrial oxygen radicals: New approaches with reactive oxygen species-sensitive probes.
AUTHOR(S): Esposti, Mauro Degli [Reprint author]; Hatzinisiriou, Irene; McLennan, Holly; Ralph, Steve
CORPORATE SOURCE: Dept. of Biochemistry and Molecular Biology, Monash University, Wellington Road, Clayton, VIC, 3168, Australia
SOURCE: Journal of Biological Chemistry, (Oct. 15, 1999) Vol. 274, No. 42, pp. 29831-29837. print.
CODEN: JBCHA3. ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 23 Dec 1999
Last Updated on STN: 31 Dec 2001

AB Investigations into the capacity of the Bcl-2 protein to prevent apoptosis have targeted mitochondria as key sites of the preventative action accorded by Bcl-2 to cells. Using novel approaches with fluorescence probes and autofluorescence detection of endogenous NAD(P)H, we have examined the effects of expressing Bcl-2 in the Bcl-2 negative Burkitt's lymphoma cell line Daudi. We evaluated for the first time the effect of Bcl-2 expression on the intracellular distribution and production of hydrogen peroxide, under basal conditions and after treatment with apoptosis inducing agents, ceramide analogs and tumor necrosis factor (TNF)-alpha. Increased availability of mitochondrial NAD(P)H was detected in Bcl-2-expressing cells and was correlated with an increased constitutive mitochondrial production of hydrogen peroxide. Although production of hydrogen peroxide was increased by either C6-ceramide or TNF-alpha in Bcl-2 negative Daudi cells commensurate with the early phases of apoptosis, this inc rease did not occur in

Bcl-2-expressing cells. Thus, Bcl-2 appears to allow cells to adapt to an increased state of oxidative stress, fortifying the cellular anti-oxidant defenses and counteracting the radical overproduction imposed by different cell death stimuli. Furthermore, we report altered cytological features of mitochondria during the early phases of apoptosis induced by C6 -ceramide and TNF-alpha. In particular, mitochondria changed in appearance, clustering in the perinuclear region and Bcl-2 expression prevented these changes from occurring.

L10 ANSWER 43 OF 44 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1998:482798 BIOSIS
DOCUMENT NUMBER: PREV199800482798
TITLE: Characterization of cytotoxicity induced by sphingolipids in multidrug-resistant leukemia cells.
AUTHOR(S): Klostergaard, Jim [Reprint author]; Auzenne, Edmond; Leroux, Elena
CORPORATE SOURCE: Dep. Tumor Biol., Box 108, Univ. Tex. MD Anderson Cancer Cent., 1515 Holcombe Blvd., Houston, TX 77030, USA
SOURCE: Leukemia Research, (Nov., 1998) Vol. 22, No. 11, pp. 1049-1056. print.
CODEN: LEREDD. ISSN: 0145-2126.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 5 Nov 1998
Last Updated on STN: 5 Nov 1998
AB Certain sphingolipids (SLs) exert fundamental roles in differentiative, growth-inhibitory and apoptotic pathways induced by a number of agents in leukemia cells. Multidrug-resistance (MDR) is a major cause of therapeutic failure in leukemia. SLs are among the diverse substrates for the MDR p-170 glycoprotein drug-efflux pump. We tested the hypothesis that expression of MDR would thereby block the cytotoxicity induced by the SLs sphingosine, sphinganine and N-hexanoyl-sphingosine. An MDR-expressing subline of murine P388 leukemia cells demonstrated an ED50 value gtoreq 2 log10 higher than the parental line in response to doxorubicin. In contrast, the ED50 values for each of the SLs were only approximately 1.5 to two-fold higher in the MDR line than in the parental; induction of DNA damage by SLs was comparable or actually greater in MDR compared to parental cells. Therefore, expression of MDR does not significantly affect the cytotoxic function of these SLs, nor do these SLs likely contribute to MDR.

L10 ANSWER 44 OF 44 BIOSIS COPYRIGHT (c) 2009 The Thomson Corporation on STN
ACCESSION NUMBER: 1996:102464 BIOSIS
DOCUMENT NUMBER: PREV199698674599
TITLE: C-2-ceramide primes specifically for the superoxide anion production induced by N-formylmethionylleucyl phenylalanine (fMLP) in human neutrophils.
AUTHOR(S): Richard, Alain; Bourgoin, Sylvain; Naccache, Paul H.; L'Heureux, Gaetan P.; Krump, Eric; McColl, Shaun R.; Pelletier, Guy [Reprint author]
CORPORATE SOURCE: Cent. Rech. Rhumatol. Immunol., Fac. Med., Univ. Laval, 2705 Boul. Laurier, Ste-Foy, PQ G1V 4G2, Canada
SOURCE: Biochimica et Biophysica Acta, (1996) Vol. 1299, No. 2, pp. 259-266.
CODEN: BBACAQ. ISSN: 0006-3002.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 12 Mar 1996
Last Updated on STN: 13 Mar 1996
AB Activated sphingomyelinases release ceramide molecules believed to be

involved in intracellular signalling. The present study investigated whether soluble C-2-ceramide modulates some of the effects of N-formylmethionylleucyl phenylalanine (fMLP) and other agonists on human neutrophils (or polymorphonuclear leukocytes-PMN); principally superoxide anion (O-2-) production. The preincubation of PMN for 15 min with C-2-ceramide increased by up to almost 3-fold the amounts of O-2- generated in response to 0.1 and 1 mu-M fMLP. Priming was detected at C-2-ceramide concentrations of 2 mu-M to 4 mu-M per million PMN. Though less potent than C-2-ceramide, C-6-ceramide (N-hexanoylsphingosine) could prime for O-2- generated in response to 0.1 AM fMLP, with maximal effects obtained at 10-20 mu-M. In contrast, micromolar concentrations of sphingosine, dihydroceramide, and ceramide-phosphate, failed to exert any potentiating effect on fMLP-induced O-2- generation. As expected, TNF-alpha (1000 U/ml), also primed for fMLP-induced O-2- production; however, the combination of TNF-alpha and C-2-ceramide showed no additive effect. Moreover, S. aureus sphingomyelinase (0.1 U/ml), was unable to reproduce the priming effects of C-2-ceramide and TNF-alpha. C-2-ceramide at 2 mu-M did not enhance the production of O-2- induced by 100 nM recombinant human interleukin-8 (IL-8), leukotriene B-4 (LTB-4), platelet-activating factor (PAF) or 20 MM sodium fluoride (NaF). Furthermore, C-2-ceramide (2 mu-M) did not enhance the mobilization of calcium, the release of arachidonic acid or the accumulation of phosphatidylethanol, induced by 100 nM fMLP. This suggests that probably neither phospholipases C, A-2 or D (PLC, PLA-2, PLD) were involved in the priming effect by C-2-ceramide. However, C-2-ceramide inhibited in a dose-related manner the production of O-2- induced by phorbol 12-myristate 13-acetate (PMA) and mezerein. Furthermore, PMA-stimulated PLD activity was also significantly reduced by a preincubation of PMN with C-2-ceramide. The priming of 2- production by C-2-ceramide could involve yet unidentified mechanisms specific for fMLP, or it might imply that cytokines such as TNF-alpha have different mechanisms than C-2-ceramide.

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=> d his

     (FILE 'HOME' ENTERED AT 15:58:06 ON 17 AUG 2009)

     FILE 'REGISTRY' ENTERED AT 15:58:30 ON 17 AUG 2009
L1             1 S C6-CERAMIDE/CN

     FILE 'CAPLUS' ENTERED AT 15:58:44 ON 17 AUG 2009
L2           252 S L1
L3            85 S L2 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM?)
L4             3 S L3 AND AD<19990407
L5            13 S L3 AND (PACLITAXEL OR TAXOL)

     FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 16:03:15 ON 17 AUG 2009

     FILE 'REGISTRY' ENTERED AT 16:03:21 ON 17 AUG 2009
                SET SMARTSELECT ON
L6           SEL L1 1- CHEM :       6 TERMS
                SET SMARTSELECT OFF

     FILE 'MEDLINE, BIOSIS, EMBASE' ENTERED AT 16:03:22 ON 17 AUG 2009
L7           596 S L6
L8           239 S L7 AND (?CANCER? OR ?TUMOR? OR ?TUMOUR? OR ?NEOPLASM?)
L9           144 DUP REM L8 (95 DUPLICATES REMOVED)
L10           44 S L9 AND (PD<19990407 OR PY<2000 OR PRD<19990407)
L11            0 S L10 AND (PACLITAXEL OR TAXOL)

=>
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---Logging off of STN---

=>
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	30.05	124.12

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	0.00	-13.12

STN INTERNATIONAL LOGOFF AT 16:11:52 ON 17 AUG 2009